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British Journal of Anaesthesia

International Journal of Anaesthesia

Volume 85 Number 3 September 2000

Editor-in-chief: Jennifer M. Hunter

- Psychomotor effects of alcohol: are they comparable with propofol?
- Perioperative management of coagulopathies
- Loss of consciousness after a spinal

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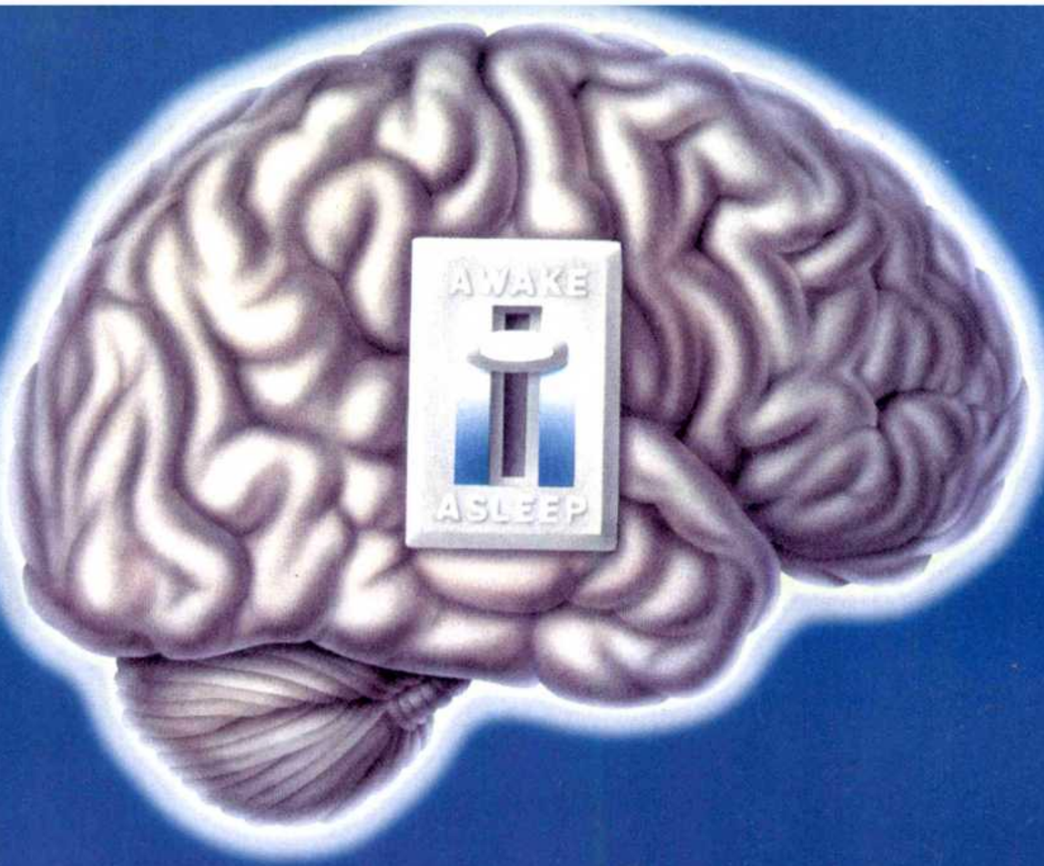

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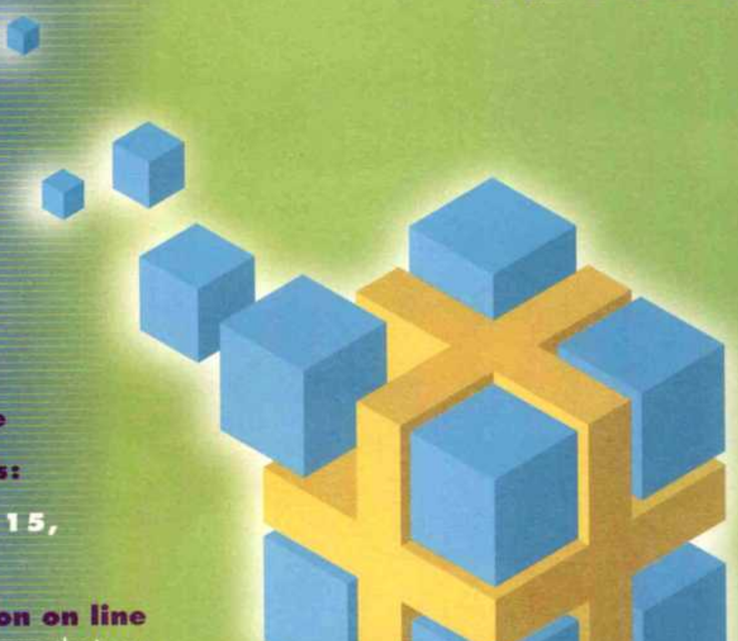

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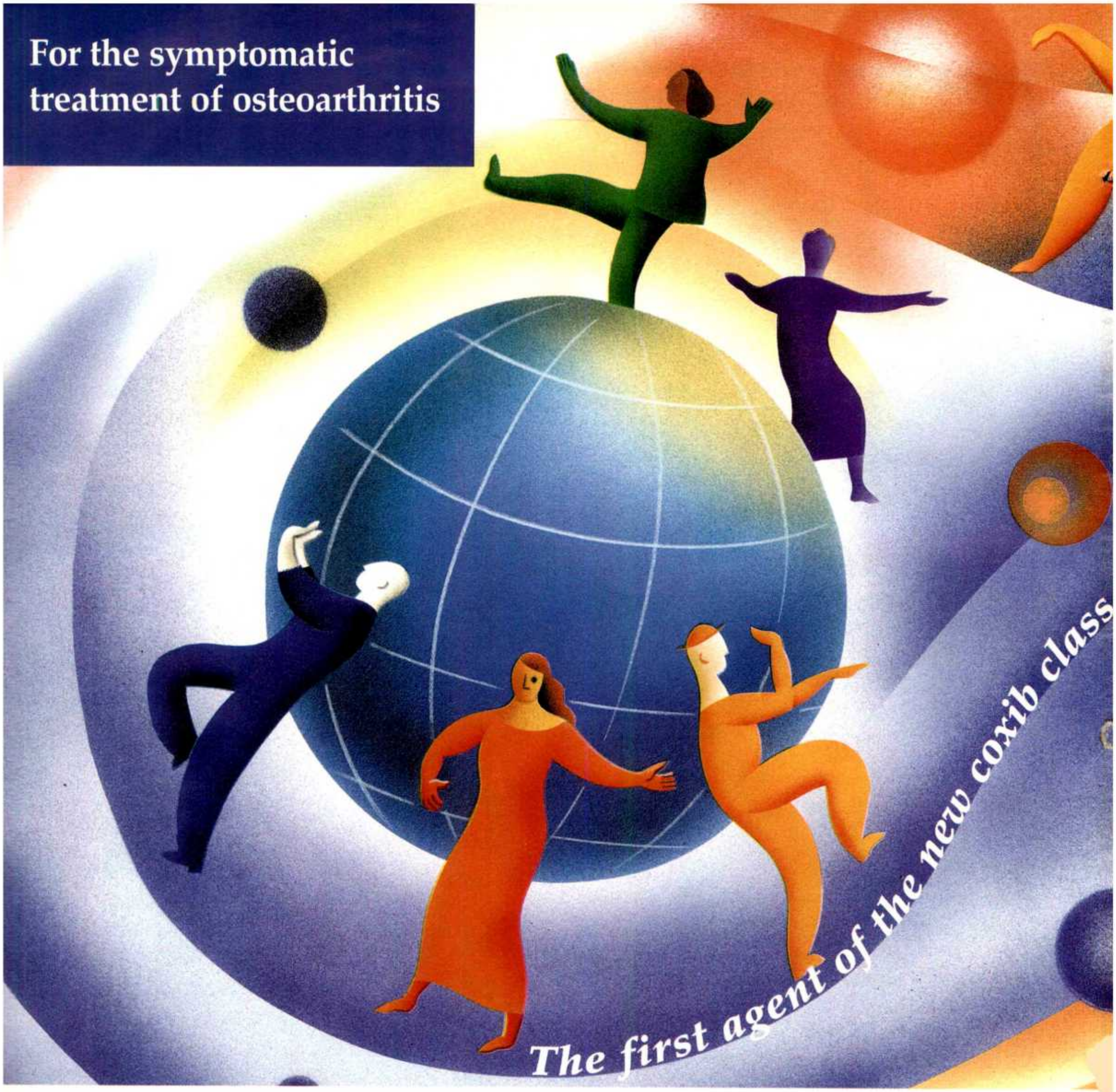

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The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

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Children: Not recommended.

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Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

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Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of

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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

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3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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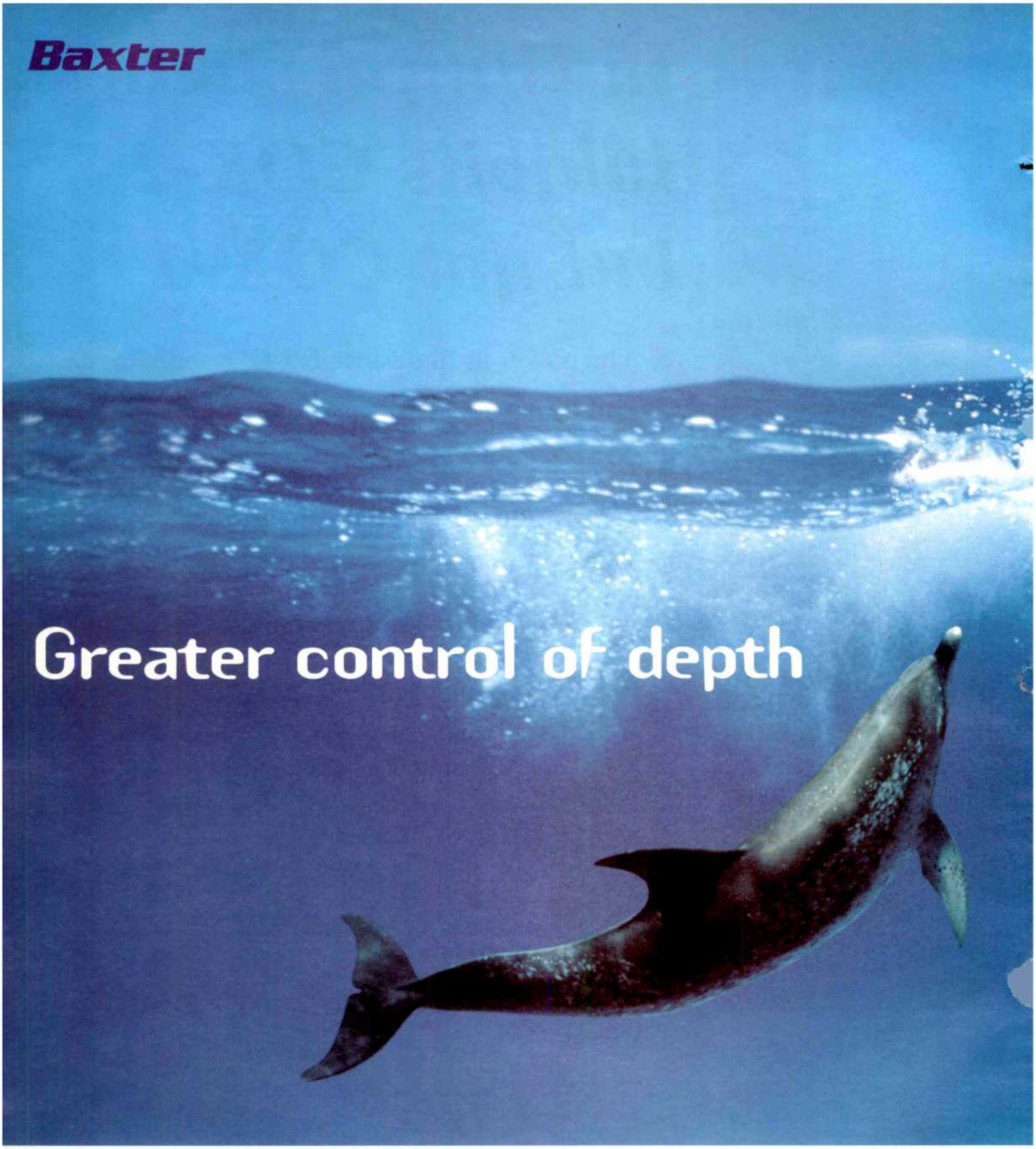
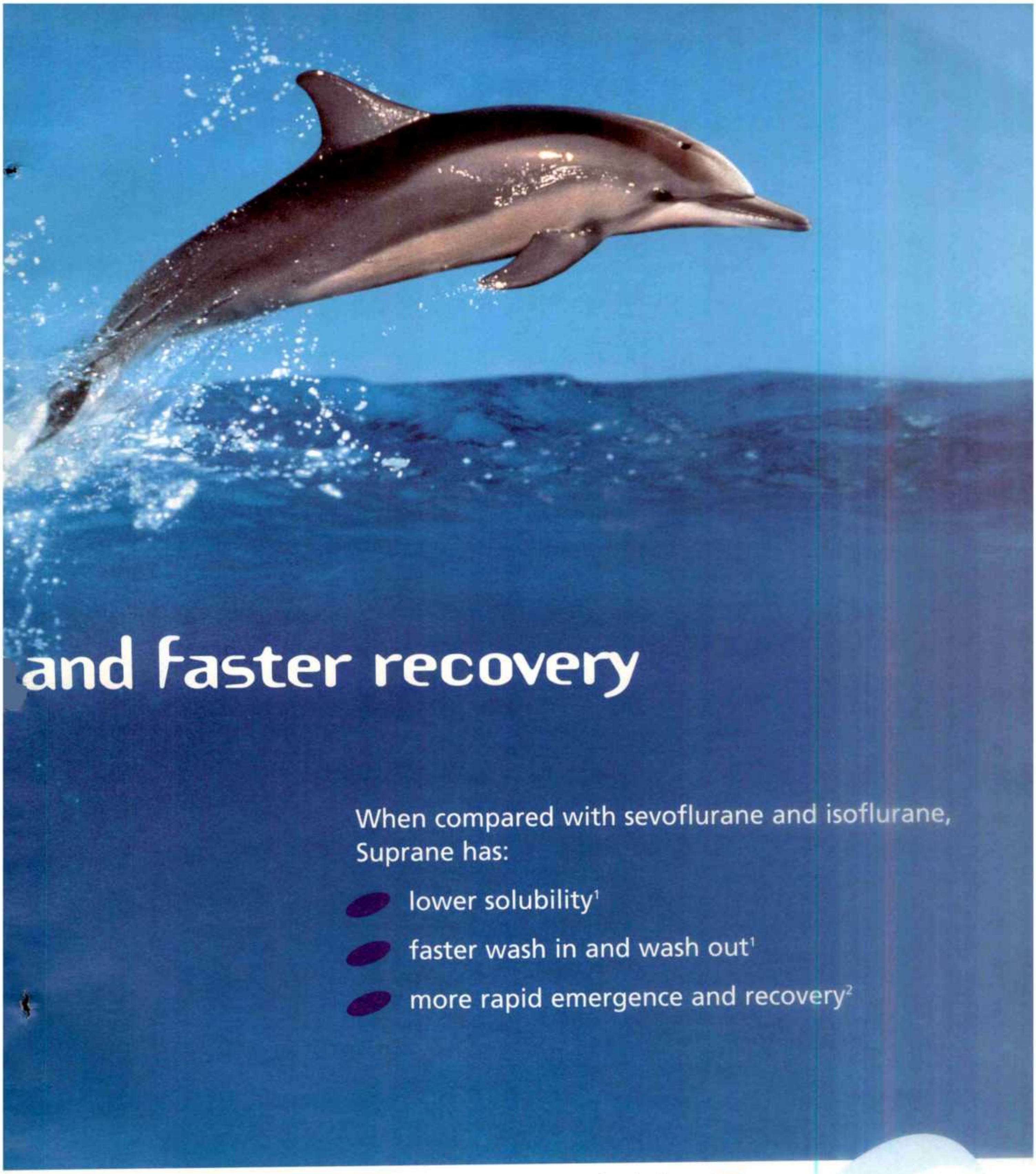


SUPRANE® (desflurane) PRESCRIBING INFORMATION **Presentation:** Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast



and faster recovery
When compared with sevoflurane and isoflurane, Suprane has:
lower solubility[1]
faster wash in and wash out[1]
more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

® Denotes registered trademark.

References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

Suprane®
desflurane

Precise control in maintenance anaesthesia

SUP021/UK/0200

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK. (PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
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*Haemoglobin levels >10 to ≤13 g/dL.

References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz M *Orthopedics.* 1999;22(suppl 1):s105-s112
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

Please see abbreviated Prescribing Information on adjacent page.

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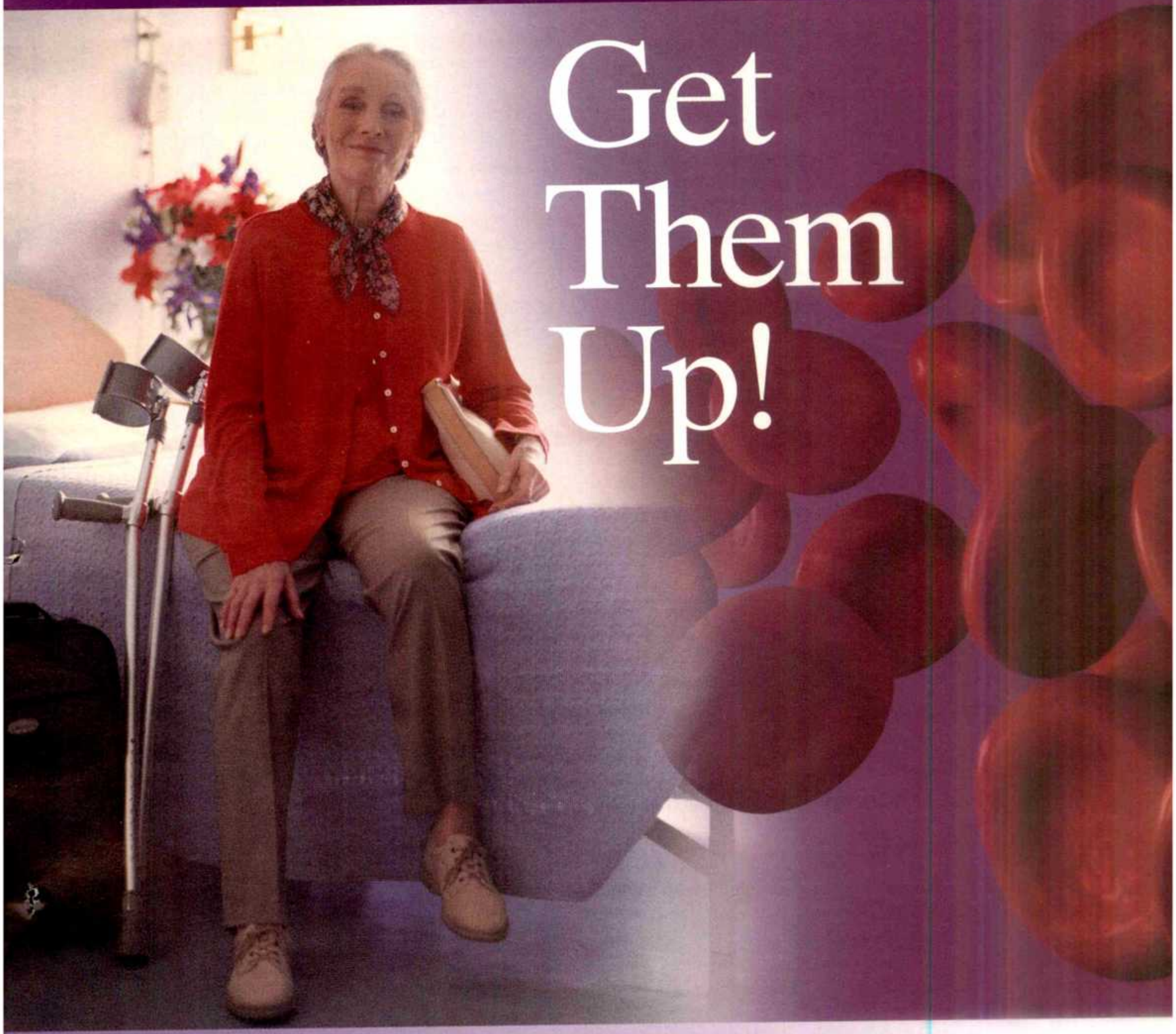

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Editorial Notices

BJA/RCA Research Fellowships

The *British Journal of Anaesthesia*, in conjunction with the *Royal College of Anaesthetists* is making a further round of grants available to support research in anaesthesia, intensive care or pain relief. The work must be conducted in the United Kingdom.

Small project grants: Grants are available to support specific research projects in anaesthetic departments. Joint applications with basic science departments will be welcome. These grants may be awarded to fund technical staff, research students or post-dostoral research fellows; salaries, or items of equipment. The maximum value of any award will be £15 000, and the *BJA/RCA* will not contribute towards overheads.

The *BJA/RCS* will not be funding Research Fellowships or Full Project Grants with this round of awards; the aim of these applications is to provide support as 'pump-priming' monies for future more substantive applications.

For further details and forms, please **WRITE** or **e-mail** to:

Dr J. W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU *or* john.sear@nda.ox.ac.uk

Closing date for applications is **OCTOBER 11, 2000**. Late applications will **not** be considered.

Anaesthetic Research Society Grants 2000

The Anaesthetic Research Society is offering three grants in the present round.

Health Family Grant: two grants up to £4000 each.

Anaesthetic Research Society Millenium Grant: one grant of up to £12000

Applicants must be members of the Anaesthetic Research Society in good standing. Grants will be administered within the United Kingdom. Applications will be considered for projects in the areas of anaesthesia, pain relief, intensive care medicine, and basic sciences related to these topics. The closing date is October 31, 2000. Further details and applications can be obtained from the grants officer: Dr M. C. Bellamy, Intensive Care Unit, St James's University Hospital, Leeds LS9 7TF, UK. Or electronically (preferred option) through ARSGrants@Livertransplant.org.uk

M.E.R.I.T. Centre Bradford Royal Infirmary, Bradford, UK – One day course in Spinal Endoscopy

Bradford, UK, 2000, September 15, 2000 and October 27, 2000

One day course with lectures, practical equipment demonstrations and observation of the technique in patients. Course material includes a comprehensive, practical guide to all aspects of the technique. Instrumentation is state-of-the-art, and it is anticipated that upon completion delegates will be in a position to consider setting up such a service in their own locality. On-going training will be offered.

Of interest to all those involved in the management and investigation of patients with back pain and sciatica as well as those involved with central neural blocks. Numbers of delegates strictly limited. Lunch will be provided.

For further information please contact:

Dr Jonathan Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford, BD9 6RJ.

Tel: +44 1274 364271/364253; Fax: +44 1274 366811; E-mail: merit.centre@mail.bradh-tr/northy.nhs.uk

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

Annual Scientific Meeting in Anaesthesiology 2000

Hong Kong, September 8–10, 2000

We have great pleasure to advise you that the captioned Meeting will be held on 8–10 September 2000 at the Sheraton Hong Kong Hotel and Towers.

Provisional Scientific Programme. Airway Workshop (Prof. David Chung); Regional Anatomy, Workshop for Regional Blocks (Prof. Phillip Bridenbaugh); Evidence Based Medicine Workshop (Dr. Florence Yap and Dr. Gavin Joynt); Keynote Lectures: Perioperative Medicine – International Perspective (Chairman: Dr T. W. Lee) (Prof. Phillip Bridenbaugh); (Prof. Mathieu Gielen); (Dr Neil MacIntyre)

Panel Discussion: Medical Liability *vs* Litigation (Chairman: Dr T. W. Lee) (Mr Douglas Jones and Mr Chris Howse). Debates (Chairman: Dr C. T. Hung) (Prof. Michael Irwin and Prof. Warwick Ngan Kee *vs* Dr Phoebe Mainland and Dr Eddie Cheam); ICU Workshop Weaning from Ventilator (Dr Neil MacIntyre).

Keynote lectures: Perioperative Medicine—International

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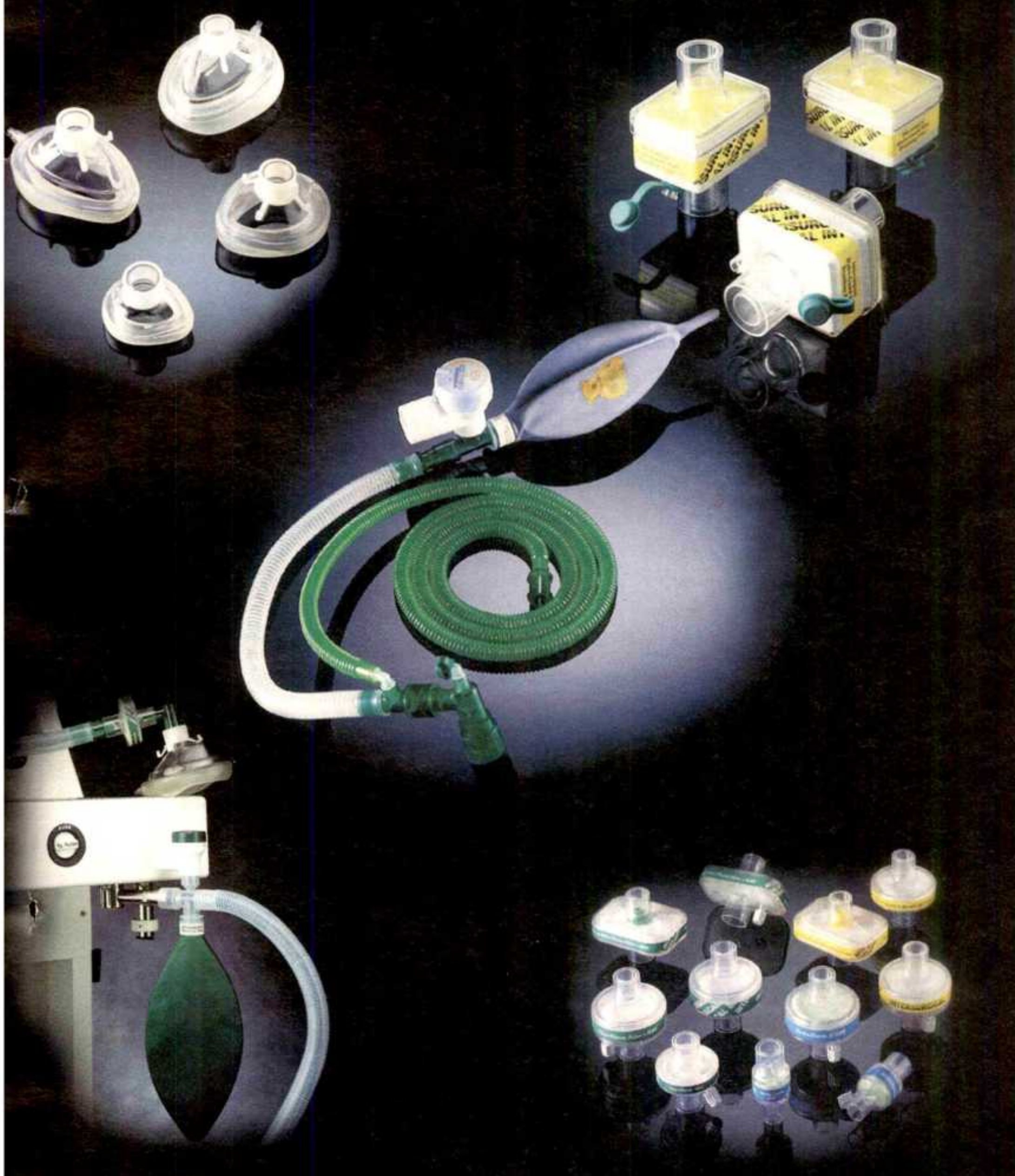

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Perspective Chairman: Dr T. W. Lee. The Road Ahead—Anaesthesiologist as Perioperative Physician (Prof. Phillip Bridenbaugh); Lung Protective Ventilatory Strategies (Dr Neil MacIntyre); Perioperative Pain Management—Comfort, Care and Cure (Prof. Mathieu Gielen).

Plenary session I. Test No Test? (Prof. Michael Irwin); Premedication—In or Out (Dr Jeffrey Kua); Perioperative Haemodynamic Goals (Dr Gavin Joynt).

Plenary session II. Preemptive Analgesia: Fact or Fallacy (Prof. Phillip Bridenbaugh); Anaesthetic Techniques—A Look into the Future (Prof Tony Gin); Continuous Spinal Anaesthesia—Is There a Role in Anaesthesia and Postoperative Analgesia (Prof. Mathieu Gielen).

Plenary session III. Chairman: Prof. Tom Buckley. Evaluation and Management of Postoperative Respiratory Insufficiency (Dr Neil MacIntyre); Acid-Base Secrets (Dr Ian Tan); Post-Anaesthetic Care—How Far Should We Go? (Dr C. T. Hung).

Refresher Course topics include: New Analgesic Agents (Dr S. L. Tsui); Anaesthesia for Cerebral Aneurysm Surgery (Dr Sathasivam Anandaciva); Advances in Clinical Measurement (Dr James Derrick); Paediatric Anaesthetic Emergencies (Prof. Cindy Aun); Day Case Anaesthesia (Dr Gwen Fok); Physiology of Consciousness (Prof. Michael Irwin); Spinal Anaesthesia for Day Surgery (Prof. Mathieu Gielen); Clinical Pharmacokinetics (Prof. Tony Gin); Anaesthesia for High-Risk Parturients (Prof. Warwick Ngan Kee); Physiology of Pregnancy (Dr K. K. Lam); Anaesthesia for Thoracic Aneurysms (Dr Das); and TEE (Dr Peter Hiong)

For further information please contact Ms Melissa Leung of the Federation of Medical Societies of Hong Kong. Tel: (852) 2527 8898; Fax: (852) 2866 7530

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

European Society for Jet Ventilation

Paris, France, September 21, 2000

The first meeting and founding general assembly of the European Society for Jet Ventilation (ESJV) will be hosted by the European Academy of Anaesthesiology Annual Meeting, Palais des Congrès, Paris (metro station 'Porte Maillot'), France.

The session is scheduled for 9.00–13.00 in room 351 (third level).

The main topics are

- Presentation and report of the 'Initiative Group Jena 2000'
- Past and present status of jet ventilation
  - Jet ventilation in airway surgery
  - Jet ventilation in minimal invasive cardiac surgery
  - Jet ventilation in experimental respiratory failure
  - Jet ventilation for radiotherapy and imaging techniques
- Presentation and discussion of the ESJV statutes
- Vote of the ESJV statutes
- Election of the ESJV board

For information please contact: Dr Peter Biro, Department of Anaesthesiology, University Hospital Zurich, Switzerland. Tel: +41 1 255 2696; Fax: +41 1 255 4409; e-mail: peter.biro@ifa.usz.ch

Collaborative Conference between Bournemouth University and Salisbury Health Care NHS Trust

Salisbury, UK, September 21, 2000

Day Surgery Conference at Salisbury District Hospital.

For further information please contact: Sam Williams, Administrative Assistant, IHCS, Bournemouth University, Royal London House, Christchurch Road, Bournemouth, BH1 3LT. Tel: +44 (0)1202 504196

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2000

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl

13th Annual Congress of the European Society of Intensive Care Medicine

Rome, Italy, October 1–4, 2000

For further information, please contact:

Fathom incorporates a new technology for the management of anaesthetic depth. Based on a clinically proven correlation between respiratory sinus arrhythmia and brainstem activity Fathom provides the anaesthetist with a real time and objective evaluation of depth.

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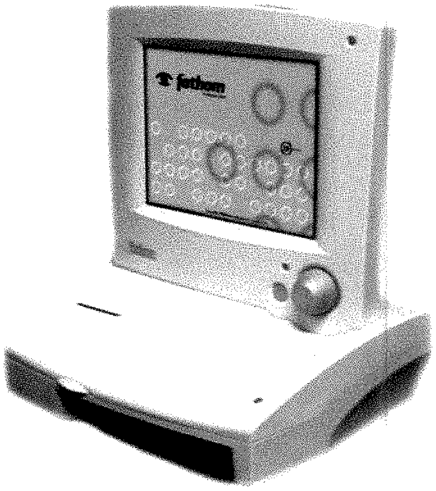

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Tel: + 32 2 559 0355; Fax: +32 2 527 0062; E-mail: public@esicm.org; Internet http://www.esicm.org

Dingle 2000 – Current Controversies in Anaesthesia and Perioperative Medicine

Dingle, County Kerry, Ireland, October 4–8, 2000

University College London Hospitals Centre for Anaesthesia announce a call for abstracts: there is an opportunity to submit work for poster presentation and selected finalists will be invited to give an oral presentation (prizes totalling £1000). Any research is acceptable provided it has not been published in any peer reviewed journal by the abstract deadline of 30 June 2000.

For further abstract and meeting registration details please contact:

Dr Monty Mythen, Centre for Anaesthesia, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK.

Tel: +44 20 7380 9477; Fax: +44 20 7580 6423;
E-mail: uch.acru@btinternet.com

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.
Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.

Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)

Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

Wood Library-Museum's Quadrennial Laureate of the History of Anesthesia Prize

Members of the Editorial team of the *BJA* are pleased to announce that, Dr Thomas B. Boulton (UK) and Dr Norman A. Bergman (USA) are to be awarded the Wood Library – Museum's quadrennial Laureate of the History of Anesthesia Prize at the annual meeting of the American Society of Anesthesiologists in October 2000, in San Francisco.

We offer our hearty congratulations to Dr Boulton, and to the family of Dr Bergman, who unfortunately died recently.

Awareness during Anesthesia—The 2000 *Anesthesiology* Journal-sponsored Symposium at the ASA Meeting

San Francisco, California, October 17, 2000, 9:00–12:30

The moderators will be Alex S. Evers MD (Washington University, St Louis) and Richard B. Weiskopf MD (University of California, San Francisco)

Awareness during anaesthesia is a potential problem of concern to clinicians and the public. There are clear cases of patients having been unintentionally awake during anesthesia and surgery and other cases for which 'awareness' was not as clearly delineated. 'Awareness' during anaesthesia and surgery can result in 'post-traumatic stress syndrome'.

This symposium will include invited speakers and a discussion session, as well as an opportunity to view selected abstracts. Abstracts in the following areas are considered appropriate for submission:

(i) epidemiology of 'awareness' during anaesthesia,
(ii) monitoring of depth of anaesthesia,
(iii) prevention of awareness during anaesthesia,
(iv) treatment of syndromes resulting from awareness during anaesthesia.

Abstracts should be submitted via the regular Annual Meeting procedures by April 1, 2000. *Online submission is available.* Abstracts requesting consideration for presentation at this symposium will undergo an additional review in addition to the standard ASA abstract review process. If you would specifically like your abstract considered for inclusion in the symposium, please check the special box that can be found on the cover letter/form which must accompany your submission. If you need abstract submission materials, please contact the American Society of Anesthesiologists:

American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068–2573, USA.

Tel: +1 847 825 5586; Fax: +1 847 825 1692;
E-mail: mail@ASAhq.org Web site: http://www.asahq.org

3rd SW Thames Anaesthesia Forum

Da Balaia, The Algarve, Portugal, October 23–26, 2000

The scientific programme will includes lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free

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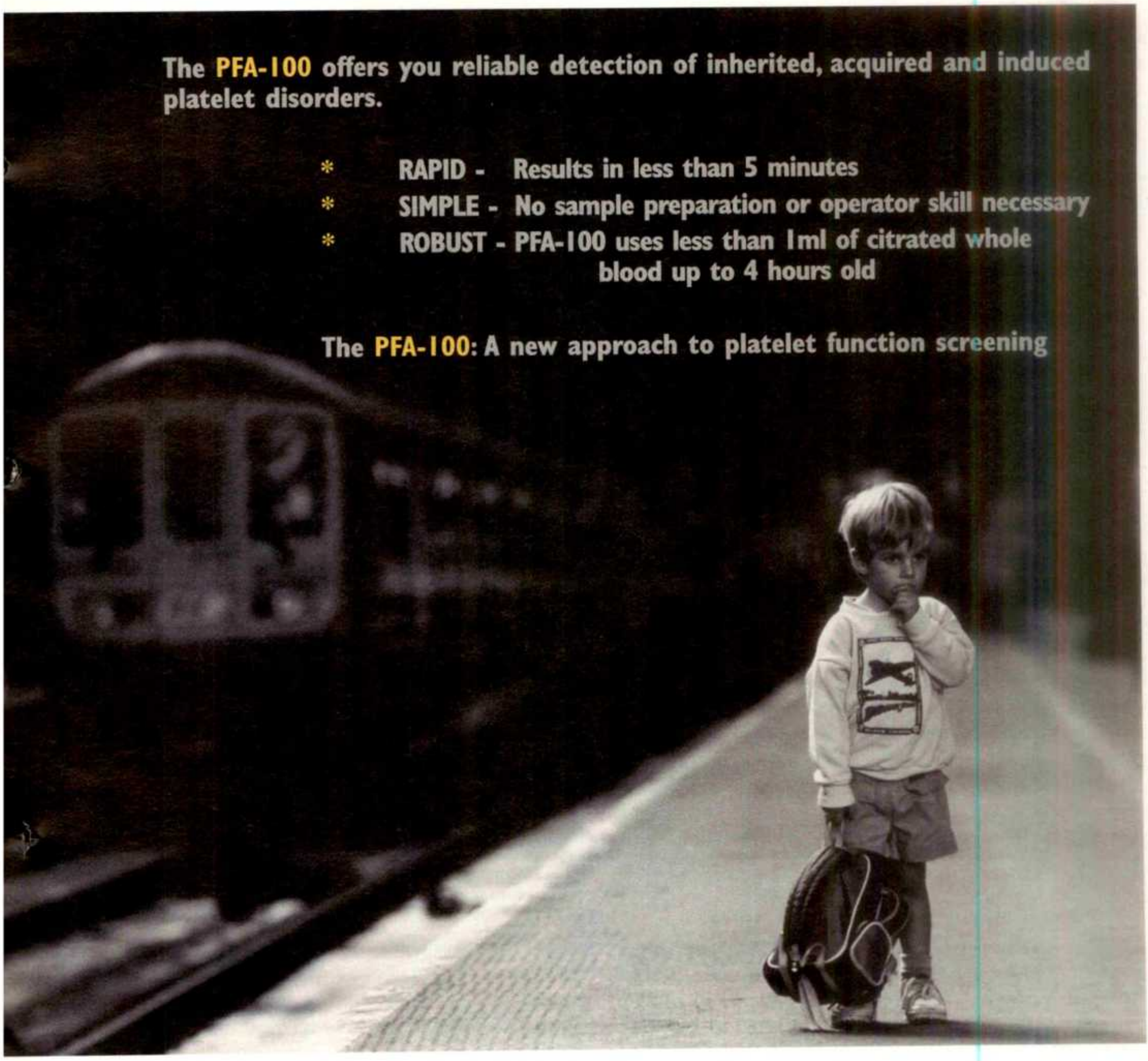

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Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: September 1st. Meeting approved for CME.

For full information and for on-line registration please visit: www.anaesthesiaupdates.com

Dr J.B.Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT.

Tel: +44(0) 20 8275 0018; Fax: +44(0) 20 8725 3135; Email: liban@mailbox.co.uk

Haemostasis and Transfusion—Perioperative Management in Elderly Patients

Graz, Austria, October 27 and 28, 2000

This symposium has been organized by the Department of Anaesthesiology and Intensive Care Medicine, University of Graz and Department of Anaesthesiology, University of Munich.

The preliminary programme includes: haemostasis and transfusion, and perioperative management in elderly patients.

For further information contact: M. Neuray/G. Taucher, Department of Anaesthesiology and Intensive Care Medicine, LKH-Universitätskinikum Graz, Auenbruggerplatz 29, A-8036 Graz, Austria.

Tel: +43 316 385 3027; Fax: +43 316 385 4664; E-mail: haemostasis@kfunigraz.ac.at. www.kfunigraz.ac.at/uanwww/haemostasis.htm

Resuscitation Fluids: Update 2000

Institute of Electrical Engineers, London, UK, November 17, 2000

Organised by the Centre for Anaesthesia, Royal Free and University College Medical School (RFUCMS), London, UK and The National Hospital, University of Oslo, Norway. This meeting has an internationally renowned faculty who will be cross examined by a panel of experts on topics including: Is albumin dead? Haemoglobin: How low can you go? Abnormal saline; The ideal colloid; Hyperoncotic/hyperosmolar; Risks of blood transfusion – oxygen carrying solutions.

Immediately following the meeting there will be a twilight trip to the 'London Eye' for all interested parties.

For further details please contact: Dr Monty Mythen, Centre for Anaesthesia RFUCMS, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London W1N 8AA, UK.

Tel: +44 (0)20 7380 9477; Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

St Bartholomew's Hospital Choral Society

Royal Albert Hall, London, UK, November 21, 2000

St Bartholomew's Hospital Choral Society celebrates the millennium and their 35th anniversary with the Royal Medical Benevolent Fund as their chosen Charity for their season 2000/2001.

Mahler's Symphony No. 8 'Symphony of a Thousand' with the Royal Philharmonic Orchestra, Royal Albert Hall, 21 November 2000.

It needs a *really* big choir, splendid orchestra, fine soloists and conductor. Six hundred singers are needed for this monumental work.

To participate contact the Barts Choir Honorary Secretary on:

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Or to support, details available from:

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Tel: +44 20 8540 9194; Fax: +44 20 8542 0494; E-mail: rm.bf@virgin.net

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.

Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

5th International Conference on Memory, Awareness and Consciousness – Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, USA, June 1–3, 2001

This conference builds on the tradition of the previous Memory and Awareness in Anesthesia Conferences, and will focus on the following topics: measurement and monitoring of memory function, awareness and consciousness; interaction of anesthetic and sedative drugs with the mechanisms of consciousness, awareness and memory processes; consequences and treatment of unwanted awareness or memory function during surgery or critical care; impact of surgery, anesthesia and critical care on cognitive and psychological processes; neuroimaging and mapping of consciousness, memory, awareness and pharmacologic effects on them in the CNS.

Deadline for abstracts: December 10, 2000.

For further information contact us via e-mail at mac@mskcc.org or visit our web site www.maacc.org or by mail: Ruth Reinsel, PhD, Dept of Anesthesiology/CCM, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10021, USA.

Tel: +1 212 639 6038; Fax: +1 212 772 8646.

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

Free Papers will be accepted for oral and poster presentation in four categories: (i) monitoring; (ii) new pharmacological agents; (iii) interesting case reports; (iv) cardiopulmonary bypass technology. Abstracts forms are available upon request. The deadline for submission is November 1, 2000. Tuition will not be waived. Brochure available in June 2000.

For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

Association of Cardiothoracic Anaesthetists

Symposium on Cardiopulmonary Transplantation
Newcastle upon Tyne, UK, February 1, 2001

Topics include: (i) Management of end-stage respiratory failure; (ii) Mechanical support for the failing heart; (iii) Cardiac transplantation; (iv) Cardiopulmonary transplantation in children; and (v) Re-perfusion injury.

For further information and registration details please contact: Dr S. R. Haynes, Department of Cardiothoracic Anaesthesia, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN, UK.

Tel: +44 (0) 191 2843111, ext: 26488; Fax: +44 (0) 191 2231175; E-mail: judith.iley@nuth.northy.nhs.uk

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)
Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail: akabogu@mcn-nuernberg.de; www: http://www. mcn-nuernberg.de

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th International Congress of Cardiothoracic and Vascular Anesthesia

19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

2nd ALL AFRICA ANAESTHESIA CONGRESS

International Convention Centre, Durban, South Africa

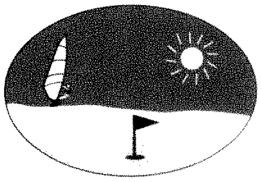
23 - 26 September 2001

CME (UK) points applied for

The above meeting is a WFSA African Regional Section Congress and will be held in conjunction with the Annual Meeting of the South African Society of Anaesthesiologists. The meeting will be preceded by a two day refresher course in anaesthesia (22nd & 23rd September 2001).

Contact Details:

SASA 2001/AAAC Congress Secretariat
Department of Anaesthetics
Private Bag 7, Congella 4013
Durban, South Africa.
Tel/Fax: +27 31 260 4472
Email: maliti@med.und.ac.za
Website: http://www.und.ac.za/med/anaesth/sasa2001.html



3rd South West Thames Anaesthesia Forum

23-26 October, 2000
(revised dates)
Da Balaia. The Algarve,
Portugal

Open to all Anaesthetists - limited to 100 participants

The Scientific Programme will include lectures, and discussions on:

- Acute and Chronic Pain
- Paediatric Update
- Day Case Anaesthesia
- Obstetric Anaesthesia
- Neurology and Anaesthesia
- ITU and Relevant Medical Topics
- Cardiothoracic topics
- Radiology for Anaesthetist
- New Drugs Update
- Training & Education
- Anaesthetic Audit
- Free papers
- Panel Discussions
- Workshops

Guest Speakers

Videos on New Equipment, Drugs and Techniques

Anaesthetists in training presenting papers are eligible for prizes.

Deadline for abstracts: August 13th 2000

This Meeting is approved for CME purposes

For further details, please contact:

Fax: 020 8725 3135
Tel: 020 8725 0018
email: liban@mailbox.co.uk

Dr J.B. Liban
Department of Anaesthesia
St George's Hospital
Blackshaw Road.
London SW17 0QT

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- COURSE -

INTENSIVE CARE TOXICOLOGY

3rd November 2000

Speakers include Intensive care specialists and toxicologists from Europe including PROF PHILIPPE LHEUREUX, Brussels, PROF FREDERIC BAUD, Paris, PROF DAG JACOBSON, Oslo and clinical toxicologists from the British Toxicology Society and the National Poisons Information Service

Course organiser: Dr Alison Jones
British Toxicology Society & National Poisons Information Service, London

The course is particularly relevant for: Specialist Registrars and Consultants in intensive care, acute medicine, clinical Pharmacology, clinical toxicology and all other intensive care professionals.

The course will address: Drugs of abuse in the ITU, care of patients with acute liver failure, the role of invasive haemodynamic monitoring, the mechanism of action of sodium bicarbonate in tricyclic antidepressant poisoning, poisoning with alcohols and the role of 4-methyl pyrazole. Other topics include the mechanism of action and use of N-acetylcysteine, the role of haemofiltration and haemodialysis and acute poisoning with hypnosedative compounds. Case orientated teaching will also be used.

CME Approved
Approved for study-leave

Registration Fee: £150

Enquiries to Annabelle Charbit, Medical Toxicology Unit, Avonley R[illegible]
[illegible] London SE14 5ER Tel 0171 771 5316 Fax 0171 77[illegible]

Abbreviated version of the International summary of product characteristics Therapeutic indications*: Esmeron is indicated as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate tracheal intubation and mechanical ventilation. **Contra-indications** Former anaphylactic reactions to rocuronium or to the bromide ion. **Special warnings and special precautions for use** Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions. Dose levels greater than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anesthetic agents or by vagal stimulation. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Because Esmeron is always used with other agents and because the occurrence of malignant hyperthermia during anesthesia is possible, even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthesia. In animal studies, Esmeron was shown not to be a triggering factor for malignant hyperthermia. **The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Esmeron:** *Hepatic and/or biliary tract disease and renal failure.* Because rocuronium is excreted in urine (up to approximately 30% within 12-24 hours) and it is expected that it is also partly excreted in bile, Esmeron should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg rocuronium bromide per kg body weight. *Prolonged circulation time.* Conditions associated with prolonged circulation time such as cardiovascular disease, old age and edematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. *Neuromuscular disease.* Like other neuromuscular blocking agents, Esmeron should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Esmeron may have profound effects and Esmeron should be titrated to the response. *Hypothermia.* In surgery under hypothermic conditions, the neuromuscular blocking effect of Esmeron is increased and the duration prolonged. *Obesity.* Like other neuromuscular blocking agents, Esmeron may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight. *Burns.* Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response. **Conditions which may increase the effects of Esmeron** Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible. Therapeutic indications may vary from country to country. *For full prescribing information see your local package insert. December 1999

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10th Annual

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February 24 - March 2, 2001
Whistler, British Columbia, Canada

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Department of Anesthesiology
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Kingston, Ontario, Canada, K7L 2V7
Voice Mail: (613) 549-6666 Ext. 3276
Fax: (613) 548-1392
E-mail: wwanesth@kgh.kari.net

OBSTETRIC ANESTHESIA CLINICAL RESEARCH FELLOWSHIPS

The Division of Obstetric Anesthesiology, Department of Anesthesiology, Columbia University, New York City has research positions available for obstetric anesthesia fellowships of one or two years duration suitable for a Senior Registrar of junior consultant seeking training for an academic career FRCA and ECFMG essential.

The fellow would be expected to do research only; but if desired, clinical patient care could be arranged. The fellow would enter an established research program involving the molecular genetics of preclampsia and premature labor, vascular alpha and beta adrenergic receptor function during normal pregnancy, pregnancy-induced hypertension and preclampsia, and other studies in the Division including ethnicity and pregnancy complications, and a variety of studies of labor and postoperative analgesia.

The positions are available January 1st, 2001 or July 1st, 2001. The Department has extensive NIH funding, and a track record of training academic clinical investigators. Excellent collaborations with the Department of Pharmacology and Obstetrics and Gynaecology exist.

Please apply with curriculum vitae to Dr. Margaret Wood, Chairman, Department of Anesthesiology, Columbia University, 622 West 168th Street (PH505), New York, NY 10032 or Dr. Richard Smiley, Director, Division of Obstetric Anesthesia, Department of Anesthesiology, Columbia University, 622 West 168th Street (PH505). New York, NY 10032 (email: rms7@columbia.edu)

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SHO in Anaesthetics

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RESUSCITATION FLUIDS: UPDATE 2000

Institute of Electrical Engineers,
London, UK ~ 17th November 2000

Organised by Centre for Anaesthesia, Royal Free and University College Medical School, London, UK and National Hospital, University of Oslo, Norway. The meeting has an internationally renowned faculty who will be cross-examined by a panel of experts on topics including:

- **Is Albumin dead?**
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- **The ideal colloid.**
- **Abnormal saline.**
- **Oxygen carrying solutions are going to be a clinical reality**

For a full programme and details of sponsored places for professionals with a specialist interest in Resuscitation Fluids please contact Dr Monty Mythen:

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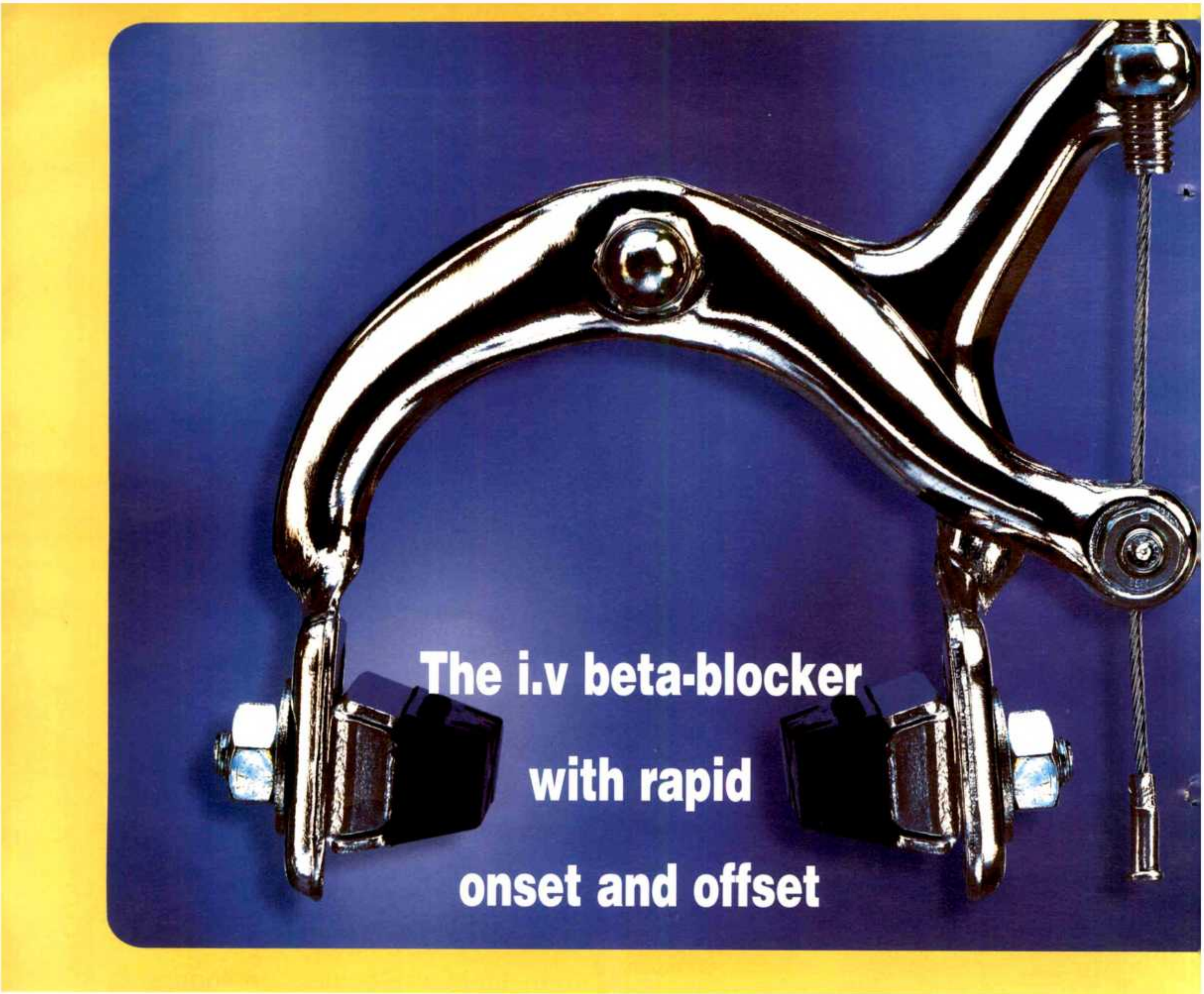

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Please refer to the data sheet before prescribing. **Presentation** Ampoules containing 2.5g esmolol hydrochloride in 10ml sterile aqueous concentrated solution (250mg/ml) to be diluted before intravenous administration. Vials containing 100mg esmolol hydrochloride in 10ml sterile aqueous solution (10mg/ml) for intravenous administration without dilution. **Uses** For the short-term treatment of tachycardia and hypertension occurring in the perioperative period and supraventricular tachyarrhythmias including atrial fibrillation, atrial flutter and sinus tachycardia. **Dosage and administration** BREVIBLOC 2.5g CONCENTRATE MUST BE DILUTED BEFORE INFUSION with an appropriate intravenous fluid to give a final concentration of 10mg/ml and infused into a large vein. Brevibloc 100mg is a ready-to-use preparation at a concentration of 10mg/ml. The following dose regimens may be used. a. For intraoperative treatment - during anaesthesia when immediate control is required, give an 80mg loading bolus over 15-30 seconds followed by a 150 micrograms/kg/min infusion. Titrate the infusion rate as required up to 300 micrograms/kg/min. b. Upon awakening from anaesthesia - administer an infusion of 500 micrograms/kg/min for four minutes followed by a 300 micrograms/kg/min infusion. c. For post-operative situations - when time for titration is available give the 500 micrograms/kg/min loading dose over one minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150, 200, 250 and 300 micrograms/kg/min given over four minutes, stopping at the desired therapeutic effect. d. For supraventricular tachyarrhythmias - give the 500 micrograms/kg/min loading dose over one minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150 and 200 micrograms/kg/min given over four minutes, stopping at the desired therapeutic effect. **Contra-indications, warnings, etc.** *Contra-indications* Brevibloc is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock and overt heart failure. There is no experience with Brevibloc in pregnancy and, although animal tests have shown no teratogenic effect, the use of Brevibloc in women where pregnancy is suspected or confirmed should be avoided. *Warnings and precautions* Use with caution in patients with bronchospastic disease or impaired renal function or diabetes. Brevibloc should also be used with caution in combination with verapamil in patients with impaired ventricular function. The combination should not be given to patients with conduction abnormalities and Brevibloc should not be administered within 48 hours of discontinuing verapamil. The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of Brevibloc. The dosage of either agent may be modified as needed to maintain the desired haemodynamics. Infus concentrations of 20mg/ml have been associated with significant ven irritation and thrombophlebitis in animals and man. Extravasation 20mg/ml may lead to a serious local reaction and possible skin necro Concentrations greater than 10mg/ml or infusion into small veins through a butterfly catheter should be avoided. *Use in Children* safety and effectiveness of Brevibloc in children have not be established. *Use in Elderly* Analysis of data from 252 patients over years of age indicated no variations in pharmacodynamic effe however no special studies in the elderly have been conducted. **Adve effects** Most frequently observed side effect has been hypotensi Other reported side effects have included bradycardia a bronchospasm. **Pharmaceutical precautions** BREVIBLOC 2 CONCENTRATE MUST BE DILUTED BEFORE USE. BREVIBLOC NOT COMPATIBLE WITH SODIUM BICARBONATE. **Legal categ** Prescription Only Medicine. **Basic NHS. price** Brevibloc 2.5g 1 Concentrate Ampoule £65.90; Brevibloc 100mg/10 ml Vial pack o £29.50. **Productlicenceholder and number** Baxter Healthcare Limit Caxton Way, Thetford, Norfolk, IP24 3SE. Brevibloc 2.5g Concentrat PL 0116/0318; PA 167/99/2. Brevibloc 100mg/10ml Vial - PL 0116/03 PA 167/99/1. **Date of Preparation** July 1998 ® Deno registered trademark

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BJA

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BRITISH JOURNAL OF ANAESTHESIA

Volume 85, Number 3, September 2000

Editorial I

Ethics in publishing; are we practising to the highest possible standards?

For new editors of scientific journals, the ethical issues involved in publishing are the most significant of the many challenges which they will face. A new world opens as they become very aware, yet again, that university did not prepare them for this venture. How should they manage such problems as dual publication, redundant publication and plagiarism? How should they define publishing misconduct?

Three years ago, to help with these problems, the Editor-in-Chief of the *British Medical Journal* (BMJ), Richard Smith, invited the editors of several specialist journals associated with this publishing group (PSP) and the editor of the *Lancet* to found a new committee, the Committee on Publication Ethics (COPE). This is a voluntary body. It aims to act as a forum for discussion and to give advice to scientific editors on practical methods of dealing with difficult issues related to publishing. It also aims to improve standards in publishing practice. It meets regularly to consider particular problems (suitably anonymized) and to advise if appropriate. Editors are invited to submit any difficult problems to the committee in writing for discussion, and hopefully this results in constructive advice.

As the new Editor-in-Chief of the *British Journal of Anaesthesia* (BJA), I was invited to join this voluntary body, and found it a useful educational exercise. The group, which is chaired by Professor M. Farthing, the Editor of *Gut*, recognized the need to produce guidelines for setting standards in the ethical issues related to publishing. After a widely advertised and detailed discussion meeting attended by over 70, mostly European, editors of scientific journals in April 1999, an advisory document was released, which is available in print[1] and through the World Wide Web (http://www.bmjpg.com/cope/contents/gpp.htm).

This document makes useful reading not only for editors but also for all potential authors interested in publishing their data. It discusses study design and ethical approval; data analysis; authorship; conflicts of interest (which the editors of the BJA are at present reviewing); peer review; redundant publication; plagiarism; the duties of editors; media relations; and advertising. It is also deals with publishing and editorial misconduct.

Guidelines on good publication practice are not new. The pharmaceutical industry has produced them for research in volunteers,[2 3] as has the Medical Research Council on the policy and procedure for inquiring into allegations of scientific misconduct.[4] But the COPE guidelines bring together all the various aspects of research ethics in a unique way. Their recommendations relate to the following eleven issues.

1. *Study design.* All research must have the approval of the local ethics committee or an alternative body, and fully informed consent must be sought. The BJA has insisted on this requirement for many years, even for the retrospective analysis of patient records and for audit studies. Statistical issues should be considered early in the design of a study, including power calculations, to ensure that an appropriate number of patients are being studied. For animal experiments, full compliance with national legislation (the 1986 Scientific Procedures Act in the UK) is essential.
2. *Data analysis.* Fabrication or falsification of data is, at all times, considered to be misconduct. Methods of analysis of whatever type must be given in sufficient detail to be reproducible. *Post hoc* analysis of subgroups which become apparent during a study is only acceptable if it is clearly disclosed. Any issues of bias developing from the methodology (for instance, a higher preponderance of female patients in a study group) must be mentioned in the discussion.
3. *Authorship.* This has proved difficult to define and has been a topic of much discussion in the BMJ.[5] All authors must be willing to take public responsibility for the contents of their paper. An intellectual contribution to the conception, design and writing up of the study must be balanced against the collection of data, such as analysis of plasma samples, and routine work such as the completion of patient questionnaires.
4. *Conflicts of interest.* The BJA is devoting more attention to the detection of this problem. At present, authors are asked to inform the Editor-in-Chief of any conflict of interest when receipt of a manuscript is first acknowledged. The *Guidelines to Authors* published in

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each issue of the journal and the *Extended Guidelines to Authors*[6] also stress the importance of such honesty. But this is inadequate, and more detailed questioning is being planned, in line with other international peer-reviewed anaesthetic journals. At present, most of the admissions of conflict I receive are of little consequence and thus are easy to admit. Do the real offenders ever confess them voluntarily?

Assessors also need to be asked in more detail to declare conflicts of interest. Conflicts may be personal (I do not like the guy); commercial (I work for the pharmaceutical industry); political (I am against the policy of a particular political party); academic (I despise these authors from another academic institution); or financial (I have been paid to write this paper). Financial interests also include travel expenses or payment of lecture fees. The BJA is intending to improve its attention to such details. However, such reporting can be taken to inane extremes, and thus become a subject of ridicule. This is apparent in reading some of the weekly medical press in Great Britain, and I wish to avoid such silliness. Nevertheless, I appreciate that, on occasions, editors themselves should declare conflicts of interest to their readers and if necessary should withdraw from the review process in relation to relevant manuscripts. This is not difficult with a journal such as the BJA, which is run by a team of editors on a daily basis, and it is practised regularly.

5. *Peer review*. The quality of a scientific journal is directly related to the quality of its peer review. I am fully aware that this is a limiting factor in the value of the manuscripts published in the BJA. Assessors must not be overburdened (and I admit to making this error on occasion), nor must they be asked to do that of which they are not capable. Assessors should be constructive in their approach, and not insulting to authors. They should aim to improve the quality of the manuscript they are reviewing and maintain confidentiality at all times. I would hope that in the near future an increasing number of BJA assessors would agree to sign their reports, as occurs in the review process for some other peer-reviewed anaesthetic journals. A few already do so. I believe, however, that this act should be voluntary.

   The COPE guidelines recommend that journals publish accurate descriptions of the peer review, selection and appeals process. The BJA editors must consider these recommendations in more detail. Regular audit of acceptance rates and publication times is also recommended. At present, these are detailed annually by the Editor-in-Chief to the BJA Editorial Board. The acceptance-to-publication interval of this journal has been 4–5 months for many years. The rejection rate is over 57% and rising with the increasing number of manuscripts submitted. If the acceptance rate were allowed to rise, each issue of the journal would increase in size and thus cost more to print and post. Hence, readers would have to be willing to pay the increased costs.

   It is entirely appropriate for authors to recommend the names of suitable assessors for their manuscripts. The editors of the BJA will often take up these suggestions, especially if they are appropriate, but will also freely use other assessors of their own choice.

6. *Redundant publication*. The publication of two or more papers from a single study without cross-reference, from the same or different departments, is very difficult to detect. It is often found only by chance and expert assessment is the major route of detection. All editors of scientific journals work constantly to detect and eradicate this problem. Full reporting of such instances in a prominent section of the journal (e.g. immediately after the editorials) is encouraged by all editors. Republication of a paper in another language, especially in the Third World, may be considered acceptable but only with prior editorial approval and with full acknowledgement at the beginning of the translated text. Authors should always disclose details of their related studies on first submission of a manuscript, including those which are in press.

   Having considered many of these details, the editors of the BJA have recently updated the *Extended Guidelines to Authors*.[6]

7. *Plagiarism*. This may occur at any stage of the research process: during the planning of a study; during data collection; on writing the manuscript; or after publication. It applies to printed or electronic reports of an investigation. Plagiarism relates to the unreferenced use of published or unpublished work belonging to other workers, including refereed grant applications. It is also relevant to work published in another language; indeed, this may be the most difficult to detect. Again, competent assessors are often responsible for detecting such fraud and editors rely on them to report it. Detection is often purely due to chance. Plagiarism is a daily concern for editors of international anaesthetic journals and is deplored by them.[7] If it is necessary to publish large amounts of any other research worker's material, permission should be sought both from author and publisher.

8. *Editorial responsibilities*. In the COPE Report, editors are noted as being stewards of their journal. This is an onerous but highly privileged position. Working under constant pressure, all editors would admit that they occasionally make incorrect decisions on whether or not to publish a manuscript. Decisions on publication should be taken only in relation to a paper's scientific contribution, originality and clarity. Particular consideration must be given to manuscripts which challenge accepted concepts; negative findings may also have significant importance. The paper should also be in the scope of the journal, a very relevant factor for the BJA. All manuscripts are considered confidential, and any

attempt to break this confidentiality should be wholly resisted by editors. Indeed, I have had to exercise such a prerogative on a few occasions. Ultimately, editors must take responsibility for correcting any flaws which are subsequently realized in a published manuscript. Corrections must be recorded prominently and as rapidly as possible.

9. *Media relations*. Although the COPE guidelines provide detailed guidance to editors on this matter, the problem is perhaps not as great for editors of anaesthetic journals as for those of weekly general medical journals. For instance, the BJA does not produce regular press releases. It must be remembered, however, that journalists may attend national meetings at which early reports of ongoing research are presented and accounts may be published without permission or clarification. Organizers of such meetings should advise speakers if they expect journalists to attend.
10. *Advertising*. This used to be a significant source of revenue for all scientific journals but in recent years it has tended to decline, especially in specialist journals. Some income is also gained from large reprint orders. It is essential that editors are not influenced in their publishing decisions by advertising revenue or reprint potential. COPE strongly advises that advertising and editorial administration are kept separate, and this has always been BJA policy. But it has been routine for the Editor-in-Chief to approve all advertisements before they are published.
11. *Misconduct*. The COPE Report provides guidelines for editorial teams on dealing with misconduct. Misconduct is defined as 'intention to cause others to regard as true that which is not true'. Deception may be intentional, or due to recklessness or negligence. Good practice at all times requires honesty and full disclosure. Editors have a responsibility always to investigate any form of misconduct. The response to such problems can at times be difficult to decide and COPE can be of particular use in this field.

    Editors do not have the legal legitimacy to conduct a thorough investigation into serious cases of misconduct. They must decide whether it is appropriate to alert the employers of an author to the misconduct, and evidence will be required. The editor must at the same time inform the authors of his/her actions. If there is no obvious employer and the authors are members of a profession, the appropriate professional body (e.g. the General Medical Council) has to be informed. An appropriate notice may also need to be inserted in the journal, especially in relation to published material.[7] The authors must always be given the opportunity to respond to such allegations. If the authors are proved guilty of wrongdoing, then editors are advised by COPE to consider taking sanctions against them. For instance, COPE advises that an editor should refuse to consider any further manuscripts for publication from the authors or their department(s) for a stated time period. For lesser offences, sanctions may be limited to a warning or may involve a formal letter to the relevant funding institution or employer detailing the problem and the action taken or proposed. An editorial is also an appropriate method of detailing any misconduct.[7] In serious cases, the paper should be withdrawn from the scientific literature by informing other editors and indexing authorities, and by placing an announcement regarding the misconduct in a prominent position in the journal.

Ethical standards in publishing continue to rise. Many of these guidelines would have been considered excessive even 10 years ago, not because they had no practical significance but because many medical researchers did not consider such activity as dual publication to be unacceptable. But attitudes have changed significantly, and for the better, as much more thought and debate have been concentrated on these issues. As Editor-in-Chief of the BJA, I am very aware that we must at all times strive to maintain high standards in anaesthesia. An advisory yet voluntary body such as COPE is a most useful reference group for any harassed, overburdened editor who aims, at times fruitlessly, to attain such high ideals.

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Editorial II

Ropivacaine in children

Ropivacaine is the s-enantiomer of a new amide local anaesthetic which has been extensively evaluated in adults and older children.[1] Recently, it has been used in younger children and several studies have reported its clinical efficacy and safety when administered for caudal epidural analgesia,[2–13] for lumbar epidural block,[14] for peripheral nerve blockade,[15,16] and as a continuous epidural infusion.[17–20] Pharmacokinetic parameters have been calculated for several different age groups and the pharmacodynamics in children are becoming clearer as clinical experience grows. A meta-analysis of neonatal outcome after maternal administration of ropivacaine has also been published recently.[21]

Ropivacaine has several properties which may be useful in paediatric practice, namely the potential to produce differential neural blockade with less motor block and reduced cardiovascular and neurological toxicity.[1] These features are particularly attractive for day case surgery in children, which is increasing in frequency.

Studies of ropivacaine in children have reported pharmacodynamics and/or kinetics after single caudal or lumbar epidural injection of doses between 1 and 3 mg kg^{-1}, peripheral nerve blockade with up to 3 mg kg^{-1}, plexus blockade, epidural infusion analgesia with up to 0.4 mg kg^{-1} h^{-1} via caudal or lumbar epidural catheters, and the effects of adding clonidine or preservative-free ketamine to caudal ropivacaine.

For single injection caudal epidural block, comparisons between equal masses of ropivacaine and bupivacaine have shown virtually identical profiles in terms of onset time, efficacy, duration of analgesia and incidence of motor blockade.[3,4,9–11,14,22] As has been demonstrated for bupivacaine, ropivacaine caudal blocks can be prolonged by a factor of 2- to 3-fold by the addition of clonidine or ketamine to the caudal injectate.[23,24] A number of studies of caudal block have compared ropivacaine with the same volume and/or mass of bupivacaine.[3,4,9–11,14,22] The 2 mg ml^{-1} concentration of ropivacaine gives results comparable to 2.5 mg ml^{-1} bupivacaine while 3.75 mg ml^{-1} solution gives less motor block than bupivacaine when equal volumes are administered. When the same mass of ropivacaine is given but in a larger volume than bupivacaine, analgesia is prolonged.[9] When a larger mass of ropivacaine is given in a similar volume, analgesia is prolonged when compared with bupivacaine or with ropivacaine itself.[12] The more concentrated solutions of ropivacaine do produce motor block but the frequency, intensity and duration is shorter than an equal mass of bupivacaine.[3,4] In a detailed study of a standard volume (1 ml kg^{-1}) of caudal ropivacaine in three concentrations (1, 2 and 3 mg ml^{-1}), the weakest solution produced a block to L4, with a shorter duration of analgesia and no motor block. Both 2 and 3 mg ml^{-1} produced higher blocks to T12 with a longer and equal duration of analgesia and motor block in 13 and 28% of children, respectively, which lasted up to 4 h. The 2 mg ml^{-1} solution appears to be optimal in terms of producing adequate analgesia with an acceptable degree of motor blockade.[2]

The pharmacokinetics of ropivacaine in children beyond 1-yr-old after a single injection caudal block are very variable but are broadly similar to those in adults and no age related effects are seen in the key kinetic parameters.[2,5,6,8,12,13,15] After single injection blocks, the plasma concentration profiles show that peak concentrations of total and free ropivacaine are well below the threshold for toxicity of 0.3–0.9 mg l^{-1}. Free fraction seldom reaches 10%. A very small proportion of the administered dose is excreted unchanged in the urine and most of the ropivacaine is excreted in the urine as hydroxylated or dealkylated metabolites. The weight-corrected values for clearance, volume of distribution and elimination half life do not vary with age between 1 and 12 yr.[2,5,6,8,12,13,15]

In younger infants, below 6 months, clearance decreases and below 3 months, significantly higher free plasma concentrations (0.099 *vs* 0.038 mg litre^{-1}) and free fractions (10% *vs* 5%) occur than in infants over 3 months old[8] after a single caudal injection of 2 mg kg^{-1} (1 ml kg^{-1} of 2mg ml^{-1} solution).

For peripheral nerve blockade, a more concentrated solution of ropivacaine, 5 mg ml^{-1}, in a volume of 0.6 ml kg^{-1} (3 mg kg^{-1}) has been found to be effective and safe in children from 1–12 yr when administered as an ilio-inguinal block.[15] This dose and route of administration resulted in low peak plasma concentrations of total ropivacaine. Maximum free plasma ropivacaine concentrations at 0.02–0.14 mg litre^{-1} were well below the toxic threshold.[15]

For single injection lumbar epidural administration in infants between 1 and 12 months,[14] a volume of ropiva-

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caine, 0.7 ml kg^{-1} (2 mg ml^{-1}) solution produced a similar onset, duration and efficacy to the same volume of bupivacaine, 2.5 mg ml^{-1}.

In this issue, Hansen and colleagues[7] have added to the body of information on the pharmacokinetics and pharmacodynamics of ropivacaine during continuous epidural infusion in children from 3 months.[7,17–20] A loading dose of 1–2 mg kg^{-1} has been described,[7,17,18,20] followed by a constant rate continuous infusion of 0.4 mg kg^{-1} h^{-1} (0.2 ml kg^{-1} h^{-1} of 2 mg ml^{-1} solution). This has been used successfully in children, infants and neonates although pharmacokinetic data are limited to those over 3 months old.[7]

Neonatal outcome after maternal administration of ropivacaine by intermittent boluses or continuous infusions compared favourably with similar doses of bupivacaine in terms of neurological and adaptive capacity scores (NACS) at 24 h, spontaneous vaginal delivery rates, instrumental delivery rates and intensity of motor block.[21]

Popliteal fossa block has been described in children with ropivacaine for analgesia after foot and ankle surgery in infants and children from 6 months.[16] The duration of effective pain relief ranged from 8 to 12 h.

In summary, for single injection caudal block, a volume of 1 ml kg^{-1} of ropivacaine 2 mg ml^{-1} solution (2 mg kg^{-1}) will reliably produce analgesia for inguinal surgery with an acceptable incidence and duration of motor block. A longer duration of analgesia can be achieved at the expense of more frequent and long lasting motor blockade by the use of a larger volume of the same concentration of ropivacaine or by using the same volume of a more concentrated solution, to a maximum dose of 3 mg kg^{-1}. Where a longer duration is needed with no motor block, clonidine, 2 μg kg^{-1} or preservative-free ketamine, 0.5 mg kg^{-1} will prolong analgesia some 2- to 3-fold. For ilioinguinal block a single injection of 3 mg kg^{-1} (0.6 ml kg^{-1} of 5 mg ml^{-1} solution) is safe and effective. For continuous epidural infusion analgesia, ropivacaine at a rate of 0.4 mg kg^{-1} h^{-1} (0.2 ml kg^{-1} h^{-1} of 2 mg ml^{-1} solution) is safe and effective. Further research is required to define the safe dosing limits in neonates, young infants and less healthy children. Clearance decreases below 6 months and protein-binding capacity in the neonate is reduced.[8] As suggested in this issue,[7] reducing the dose and limiting the duration of continuous infusions to 36–48 h are recommended in neonates and young infants until further data are available.

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BJA

CLINICAL INVESTIGATIONS

Pharmacokinetics and clinical efficacy of long-term epidural ropivacaine infusion in children[†]

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The clinical efficacy and pharmacokinetics of long-term epidural ropivacaine infusion were investigated in 18 postoperative children aged between 0.3 and 7.3 yr. A lumbar or thoracic epidural catheter was inserted after the anaesthetic induction. Sixty minutes following a bolus dose of ropivacaine 1 mg kg^{-1}, 0.2% ropivacaine was infused at a fixed rate of 0.4 mg kg^{-1} h^{-1} for a mean of 61.3 h (range 36–96 h). Clinical evaluation comprised hourly recording of pain, sedation, motor block, nausea/vomiting, pruritus-scores, Sp_{O_2}, pulse and respiratory rates, and recording of non-invasive arterial pressure every 4 h. Total and free plasma concentrations were measured by high-performance liquid chromatography at 0, 1, 6, 12, 24, 36, 48, 72 and 96 h. Analgesia was of high quality and side effects were minor. No clinical signs of local anaesthetic toxicity were seen. Total (100–3189 μg litre^{-1}) and free (10–56 μg litre^{-1}) ropivacaine concentrations were within the range reported to be 'safe' in previous studies in adults. Mean (95% CI) volume of distribution was 3.1 litre kg^{-1} (2.1–4.2 litre kg^{-1}), total clearance was 8.5 ml kg^{-1} min^{-1} (5.8–11.1 ml kg^{-1} min^{-1}), free clearance was 220 ml kg^{-1} min^{-1} (170–270 ml kg^{-1} min^{-1}) and elimination half-life was 4.9 h (3.0–6.7 h).

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Ropivacaine, a new long-acting aminoamide local anaesthetic, has been shown to have a lower potential to produce central nervous system and cardiovascular toxicity and to reduce motor block in adults compared with bupivacaine.[1–4] Hence, ropivacaine may be the ideal local anaesthetic for epidural infusion in paediatric patients.

To date, ropivacaine has not been approved for the use in children under the age of 12 yr and only a few paediatric studies of epidural (i.e. caudal bolus doses) ropivacaine have been reported.[5–11] The concept of epidural ropivacaine infusion in children has been addressed in a letter,[12] but no data are available describing the pharmacokinetics of continuous long-term epidural ropivacaine infusion in children.

The aims of this study were to determine the clinical efficacy, plasma ropivacaine (total and free) concentrations and pharmacokinetics of long-term continuous epidural infusion in children following major surgery. An open design was chosen because continuous epidural use of the drug in children had not been studied previously.

Patients and methods

Patients and drug administration

After approval by the Princess Margaret Hospital Ethics Committee and written informed parental consent, 18 children (ASA I–II, age >3 months, <8 yr) undergoing major elective abdominal, urologic or orthopaedic surgery were included in this study. Apart from EMLA, no

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premedication was given to any of the children. General anaesthesia was induced with either 8% sevoflurane in oxygen or i.v. propofol 3–5 mg kg^{-1}, and endotracheal intubation was facilitated by vecuronium (0.1 mg kg^{-1}). Anaesthesia was maintained with oxygen (35%), nitrous oxide (65%), isoflurane (0.5–1.0%) and i.v. fentanyl (2–5 μg kg^{-1}).

A 0.9-mm (~20-gauge) epidural catheter was inserted via the lumbar or low thoracic route under sterile conditions using a 18-gauge Tuohy needle (Portex Minipack System, Hythe, Kent, UK) and a 'loss-of-resistance' technique with normal saline. The level of the insertion depended on the type of surgery. Correct placement of the catheter was confirmed by negative aspiration of blood and cerebrospinal fluid. No test dose was used.

Before surgery, a bolus dose of 0.5 ml (1 mg) kg^{-1} 0.2% ropivacaine (Naropin, Astra Pharmaceuticals, NSW, Australia) was given over a period of 10 min. Sixty minutes later, a continuous infusion of 0.2% ropivacaine was commenced at a rate of 0.4 mg kg^{-1} h^{-1}. No extra bolus doses were allowed. Paracetamol 15–20 mg kg^{-1} p.o. or p.r. was given every 6 h as additional analgesia. If pain scores were >3/10, rescue analgesia with i.v. bolus doses of morphine 25 μg kg^{-1} was given. Intraoperative fluid management comprised Ringer's lactate at a rate of 5–10 ml kg^{-1} h^{-1}.

Postoperatively, all children were monitored according to a protocol comprising hourly recording of pulse and respiratory rates, Sp_{O_2}, observational pain score (numerical 0–10), sedation score (X=normal sleep, 0=awake and alert, 1=drowsy, rousable to verbal commands, 2=drowsy, rousable to shaking, 3=unrousable), motor block score (0=no movement, 1=ankle only, 2=ankle and knee, 3=ankle, knee and hip), postoperative nausea and vomiting score (0=nil, 1=resolved without treatment, 2=respond to treatment, 3=no response to treatment), and pruritus score (0=nil, 1=mild, respond to topical treatment, 2=moderate, respond to systemic treatment, 3=severe, despite systemic treatment). Arterial pressure was measured non-invasively at every 4 h.

All children had an urinary catheter inserted intraoperatively. Specific problems such as drug errors, equipment malfunction and epidural catheter-related problems (disconnection, leakage, local inflammation and pressure areas) were recorded.

Blood sampling

Venous blood samples (1.5–2 ml) were taken from a peripheral i.v. catheter (20- or 22-gauge, Insyte™, Becton Dickinson Infusion Therapy Systems, Sandy, UT, USA). A baseline sample was taken after induction, and further samples were taken at 1, 6, 12, 24, 36 and 48 h after the start of the infusion, or for as long as sampling from the cannula was possible. If the ropivacaine infusion continued beyond 48 h, additional samples were taken every 24 h. After each blood sampling, the i.v. catheter was flushed with heparinized saline (1–2 ml). Blood samples were separated by centrifugation at 1500 *g* for 5 min and plasma stored at –20°C prior to assay.

Measurement of total ropivacaine concentration

Following the addition of bupivacaine (300 ng) as an internal standard, 0.5 ml plasma was adjusted to pH 9.2 by the addition of 0.5 ml 2% sodium tetraborate, and the analytes were extracted into 10 ml diethylether by shaking vigorously for 5 min. After centrifugation (2000 *g* for 5 min), the organic phase was back-extracted into 0.2 ml 0.1 M H_2SO_4 by shaking well for 1 min. After discarding the organic phase, aliquots of the acid were injected onto the HPLC. The HPLC system consisted of a Merck LiChrospher RP Select B column (250×4 mm) and a solvent of 25% acetonitrile in 45 mM phosphate buffer pH 3. Eluting compounds were detected by their absorbance at 220 nm. Plasma ropivacaine concentrations were interpolated from a plot of peak height ratio (ropivacaine : bupivacaine) versus ropivacaine added to blank plasma (0–1200 μg $litre^{-1}$). The correlation coefficient over the concentration range 100–800 μg $litre^{-1}$ was 0.9999. The coefficient of variation over the concentration range 150–700 μg $litre^{-1}$ was between 1.5 and 2.5%, and the limit of quantification was 10 μg $litre^{-1}$. Samples above the highest concentration of the standard curve were re-assayed using smaller aliquots to ensure that the assays fell within the stated range.

Measurement of free plasma ropivacaine concentration

Free ropivacaine in plasma was assayed after ultrafiltration using Amicon Centrifree YM-30 centrifugal filter (Millipore, MA, USA). Aliquots of the ultrafiltrate (0.25 ml) were then extracted and analysed by HPLC as above. Ultrafiltrate ropivacaine concentrations were interpolated from a plot of peak height ratio (ropivacaine : bupivacaine) versus ropivacaine added to blank plasma ultrafiltrate (0–75 μg $litre^{-1}$). The correlation coefficient over the range 15–75 μg $litre^{-1}$ was 0.998. The coefficient of variation for the concentration range 15–75 μg $litre^{-1}$ was between 2.6 and 7.4%, and the limit of quantification was 10 μg $litre^{-1}$.

Pharmacokinetic analysis

A one-compartment model with sequential bolus and infusion inputs was fitted (unweighted) to the total plasma ropivacaine concentration–time data[13] to give estimates of elimination half-life ($t_{\frac{1}{2}}$), apparent total clearance (Cl_t/F) and apparent volume of distribution (V_d/F). C_{max} (free and total) was defined as the highest concentration achieved during the time at which the infusion regimen had achieved a steady-state. The free fraction for ropivacaine in plasma (fµ) was calculated from measurements of three to seven different samples for each individual patient. Free ropivacaine clearance (Cl_f/F) was calculated as (Cl_t/F)/fµ.[14]

Statistical analysis

Patient characteristics and plasma (total and free) ropivacaine concentrations are summarized as mean (range), and fµ data (as percent) are summarized as median (range). Derived pharmacokinetic data are summarized as mean (95% CI). Correlation between age and pharmacokinetic parameters was investigated using linear regression analysis. Kruskal–Wallis one-way ANOVA was used to examine fµ across the six sampling times (1–48 h). A value of $P<0.05$ was considered significant.

Results

Eighteen children (nine females) were included in the study (Table 1). Their mean age was 3.3 yr (0.3–7.3 yr) and mean weight was 15.5 kg (6–30 kg). The epidural catheter was inserted at a low thoracic level in seven and at a lumbar level in 11 children. The mean duration for the epidural infusion was 61.3 h (36–96 h). The mean sampling time was 49.3 h (24–96 h). In patient 9, the epidural catheter fell out after 40 h. In patient 12, the infusion was stopped after 48 h. However, 3 h later he experienced severe pain, which was treated with an 8-ml bolus of 0.2% ropivacaine followed by recommencement of the epidural ropivacaine infusion for an additional 24 h. No blood samples were taken from this child after this event.

Clinical efficacy

The epidural blocks obtained were considered successful in all the children, as they achieved adequate intra- and postoperative analgesia, and completed the study without complications or signs of clinical toxicity. None of the children required transfusion of blood or blood products.

Arterial pressure, pulse rate, respiratory rate and Sp_{O_2} remained stable throughout the study period in all children. Overall, pain scores were <3/10. Six patients were given one to four bolus doses of morphine during the first 24 h postoperatively, because of distress rather than pain. Patient 7 needed three bolus doses of morphine over a period of 24 h following the cessation (at 72 h) of the epidural ropivacaine infusion. Due to the age of patient 17 (3.5 months), the epidural ropivacaine infusion was stopped after 48 h and a morphine infusion comprising 10 µg kg^{-1} h^{-1} was initiated for a further 24 h.

When not asleep, all the patients had a sedation score <1. Four patients had a total of five episodes of postoperative nausea and vomiting which was alleviated by the administration of ondansetron. Patient 4 vomited intermittently throughout the entire study period despite the administration of ondansetron, metoclopramide and trimeprazine. Patients 5 and 14 had a motor block score of 2 for the first 24 h postoperatively and, after that, their motor block score increased to, and stayed at, 3 for the rest of the infusion period. The remaining 16 patients had a motor block score of 3 throughout the entire study period. None of the children suffered any pruritus. During the entire study period, patient 4 intermittently showed jerky movements of her legs when asleep.

Pharmacokinetic data

A one-compartment open model with an infusion input was fitted to the data for 15 patients. Figure 1A–C shows plasma ropivacaine (total and free) concentration–time profiles for patients 6, 9 and 16 who were typical of the group. Data from three patients could not be analysed

Table 1 Patient characteristics

Patient no.	Age (yr)	Gender	Weight (kg)	Surgery	Duration of infusion (h)
1	0.6	M	9.0	pyeloplasty	36
2	4.6	M	13.5	r/o osteoid osteoma femur	48
3	3.4	M	17.5	ureteric reimplantation	72
4	2.3	F	13.5	ureteric reimplantation	48
5	3.4	F	14.5	r/o Wilm's tumour	72
6	7.2	F	30.0	ureteric reimplantation	72
7	1.8	M	15.0	r/o Wilm's tumour	72
8	3.7	F	14.5	pyeloplasty	48
9	1.8	F	12.5	nephrectomy	36
10	4.0	F	18.5	ureteric reimplantation	96
11	5.5	F	16.0	ureteric reimplantation	92
12	7.3	M	26.0	pyeloplasty	76
13	1.5	F	10.0	vaginoplasty	48
14	6.4	F	24.4	ureteric reimplantation	72
15	0.8	M	10.0	ureteric reimplantation	48
16	3.1	M	18.0	ureteric reimplantation	72
17	0.3	M	6.0	Duhamel's pull-through	48
18	1.7	M	10.5	ureteric reimplantation	48

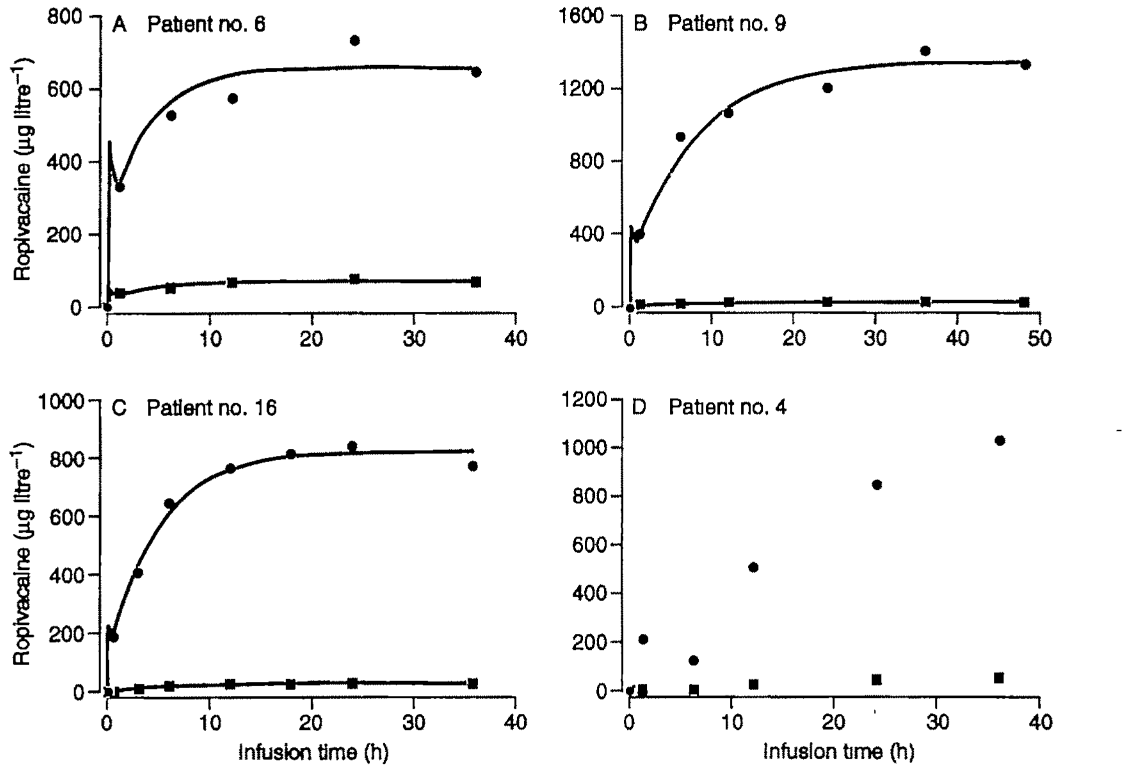

Fig 1 Plasma concentration–time profiles for total (●) and free (■) ropivacaine in patients 6 (A), 9 (B), 16 (C) and 4 (D) The solid lines show the computer-generated line of best fit for a one-compartment open model with an initial epidural ropivacaine bolus dose of 1 mg kg^{-1} over 10 min, followed by an epidural ropivacaine infusion of 0.4 mg kg^{-1} h^{-1}. Patient 4 (D) did not reach steady-state and the pharmacokinetic model therefore could not be fitted to the data.

Table 2 Total (C_t) and free (C_f) plasma ropivacaine concentrations (mean and range) and percent free unbound (fµ) for ropivacaine (median and range) at different time points during continuous epidural infusion in children

Hours after start	0	1	6	12	24	36	48	72	96
C_t	< 5	408	619	809	1063	1109	1077	925	933
(µg litre^{-1})		(102–719)	(149–1256)	(298–1638)	(312–2329)	(392–3167)	(204–3189)	(690–1277)	—
C_f	—	21	26	26	28	29	27	22	—
(µg litre^{-1})		(10–56)	(10–54)	(12–48)	(16–47)	(17–51)	(17–52)	(14–29)	
fµ	—	5.2	3.3	2.5	2.8	2.7	2.1	—	
		(1.9–12.9)	(1.6–10.2)	(1.4–8.4)	(1.4–5.7)	(1.6–8.5)	(1.6–4.0)	(2.0–3.8)	

Table 3 Pharmacokinetic descriptors for ropivacaine pharmacokinetics following epidural infusion in children (data as mean ± 95% CI). V_d/F=volume of distribution/absorption, K_{el}=elimination constant, $t_{\frac{1}{2}}$=elimination half-life, Cl_t/F=total clearance/bioavailability, Cl_f/F=free clearance/bioavailability, fµ=% free ropivacaine

Pharmacokinetic data V_d/F (litre kg^{-1})	K_{el} (h^{-1})	$t_{\frac{1}{2}}$ (h)	Cl_t/F (ml kg^{-1} min^{-1})	fµ (%)	Cl_f/F (ml kg^{-1} min^{-1})
3.1	0.233	4.9	8.5	4.2	220
(2.1–4.2)	(0.133–0.333)	(3.0–6.7)	(5.8–11.1)	(2.7–5.7)	(170–270)

by the above method. Patient 4 (Fig. 1D) did not reach steady-state during the course of the study, and in patients 8 and 17 there were insufficient data points for a robust analysis.

Mean (range) ropivacaine concentrations (total and free) and the median (range) % of free unbound ropivacaine from all the children studied are stated in Table 2. Total plasma ropivacaine concentrations were mainly low and within or below limits reported to be 'safe' in adults (1000–3000 µg litre^{-1}).[4 15–22] In the majority of the children, concentrations had reached steady-state within 36 h. Mean (range) $C_{max,total}$ was 1202 µg litre^{-1} (312–3189 µg litre^{-1}). The greatest individual total plasma ropivacaine concentration (3189 µg litre^{-1}) was measured at 48 h. This patient (17) was the youngest in our group (3.5 months) and we deliberately did not want to continue the epidural ropivacaine infusion

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Is obstructive sleep apnoea a rapid eye movement-predominant phenomenon?

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Obstructive sleep apnoea (OSA) is thought to be worse during rapid eye movement (REM) sleep. REM rebound in the late postoperative period can follow the REM suppression shown to occur after some types of surgery. This is thought to worsen nocturnal episodic hypoxaemia, leading to greater cardio-respiratory risk. We set out to determine if OSA was a REM-predominant phenomenon. We reviewed the sleep clinic records of 64 consecutive patients with a diagnosis of OSA on full overnight polysomnography and sufficient data to determine the presence of a sleep stage predominance. OSA was diagnosed if the number of apnoeas/hypopnoeas per hour of sleep, the respiratory disturbance index (RDI), was greater than 10. The variables recorded for the purposes of this study were the RDI and the minimum blood oxygen saturation using pulse oximetry ($Sp_{O_2,min}$) for both REM and non-rapid eye movement (NREM) sleep. All values are presented as mean (SD). The Wilcoxon signed rank test was used for statistical analysis. The means for NREM and REM RDI were, respectively, 36 (26) and 38 (27) per hour (P=0.96). In 32 of the 64 patients (50%) the RDI in NREM was greater than in REM. Thirty-one (48%) had a larger number during REM. One patient had identical RDIs for both REM and NREM. Sixty-two patients had satisfactory pulse oximetry recordings for both NREM and REM, and the mean $Sp_{O_2,min}$ values were, respectively, 84 (7) and 82 (13)% (P=0.15). Twenty-nine patients (47%) had a lower $Sp_{O_2,min}$ in REM (seven by more than 10% and two by more than 40%), while 24 (39%) were lower in NREM (two by more than 10%). Nine patients (14%) had identical values in REM and NREM. In contrast to suggestions that OSA is a REM-predominant phenomenon, this study suggests that respiratory disturbance is not greatly affected by sleep stage, in most patients. While a small number clearly desaturate much more during REM, the majority do not. Thus, postoperative REM rebound may worsen OSA in some patients, but in many it may do otherwise. The implications of postoperative sleep disturbance are therefore likely to be more complex than previously suggested.

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Anaesthetic articles suggest that obstructive sleep apnoea (OSA) is a rapid eye movement (REM)-predominant phenomenon, and that REM rebound in the late postoperative period, which follows REM suppression after some types of surgery, can worsen nocturnal episodic hypoxaemia.[1–5] The results of the first preoperative polysomnogram (PSG) carried out as part of another investigation currently in progress suggested that this might not always be the case. This particular patient had previously undiagnosed, mild obstructive sleep apnoea, which was non-rapid eye movement (NREM) stage two predominant.

To determine if this was an isolated finding, the records of a consecutive series of 148 unselected patients seen in consultation by one of the authors (J.L.) in the Sleep Disorders Consultative Service at the Royal Prince Alfred Medical Centre (Sydney, Australia) were reviewed.

Patients and methods

Patient selection

The medical records of 148 consecutive new patients seen by one physician (over a period of ~2 yr) in a sleep disorders

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clinic were reviewed retrospectively. The patients referred to the clinic are assigned randomly, according to time available on a first come first served basis, to one of several physicians by the secretarial staff when the booking is made.

Eleven of the records were unavailable at the time of the review. Twenty-nine patients were still waiting for their diagnostic sleep studies (DSS), and three had failed to attend.

Of the 105 patients who had already undergone DSS, 20 had an overall respiratory disturbance index (RDI – the number of apnoeas and hypopnoeas per hour of sleep) of less than 10 per hour (considered normal), 10 had a non-OSA diagnosis (narcolepsy for example) and 10 had OSA but the REM/NREM differential for the RDI and minimum blood oxygen saturation ($Sp_{O_2,min}$) were not reported. One patient had no REM sleep on the night of the study. Sixty-four patients who had OSA and sufficient information to identify any sleep stage predominance therefore remained for inclusion in the study.

The variables recorded were the RDI and the minimum blood oxygen saturation using pulse oximetry ($Sp_{O_2,min}$) for both REM and non-rapid eye movement (NREM) sleep, as well as any demographic data available. A number of the study reports lacked satisfactory body position data, and this factor was not included in the analysis. Four patients had a previous diagnosis of asthma. Spirometric data were recorded for all but 11 patients. Three had an FEV1/FVC of less than 70%, two of whom had no known previous history of lung disease.

Diagnostic sleep study

The diagnostic sleep studies performed in each case were overnight polysomnographic studies including electroencephalogram (C4/A1, O2/A1), electro-oculogram, submental and diaphragm electro-myogram, nasal airflow, chest and abdominal strain gauge, pulse oximeter, electrocardiogram, leg movement sensors and position sensor. All diagnostic studies were carried out in a variety of sleep laboratories independent of the clinic and analysed manually, according to standard criteria, by experienced sleep study technicians, and further checked by one of several physicians specializing in sleep medicine. All episodes of oximetry artefact were manually rejected from analysis. No studies were scored by the authors.

Definitions

OSA was diagnosed if the overall RDI was greater than 10 per hour. While a small number of patients experienced some central events, there were no patients in this study with enough central apnoea to classify them as having either mixed or predominantly central sleep apnoea (CSA).

Statistics

All values are presented as mean (SD) unless otherwise stated. The Wilcoxon signed rank test was used for statistical analysis.

Results

Respiratory disturbance index

The mean values for NREM and REM RDI were, respectively, 36 (26) and 38 (27) per hour (P=0.96). In 32 of the 64 studies (50%), the RDI in NREM was greater than in REM. Thirty-one (48%) had a larger number during REM. One patient had identical values for both REM and NREM. The REM versus NREM value for each patient is plotted in Fig. 1.

Minimum saturation

Two patients did not have the $Sp_{O_2,min}$ recorded for one or both of REM or NREM, leaving 62 for analysis. The mean values for NREM and REM $Sp_{O_2,min}$, respectively, were 84 (7) and 82 (13)% (P=0.15). Twenty-nine patients (47%) had a lower $Sp_{O_2,min}$ in REM (seven by more than 10% and two by more than 40%), while 24 (39%) were lower in NREM (two by more than 10%). Nine patients (14%) had identical values in REM and NREM. The REM versus NREM value for each patient is plotted in Fig. 2. Those patients with the lowest overnight saturation had a tendency for this to occur during REM, while the milder apnoeics had similar nadirs for both REM and NREM.

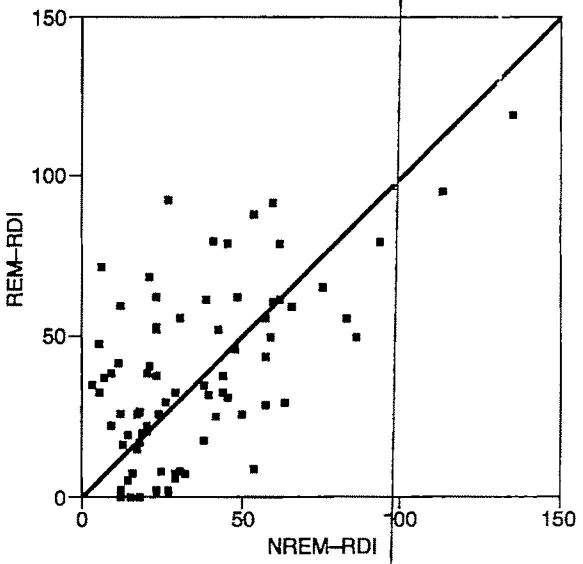

Fig 1 The respiratory disturbance index (events per hour) in REM plotted against the respiratory disturbance index in NREM for each individual patient in the study. Those above the diagonal represent patients with a higher RDI during REM and vice versa

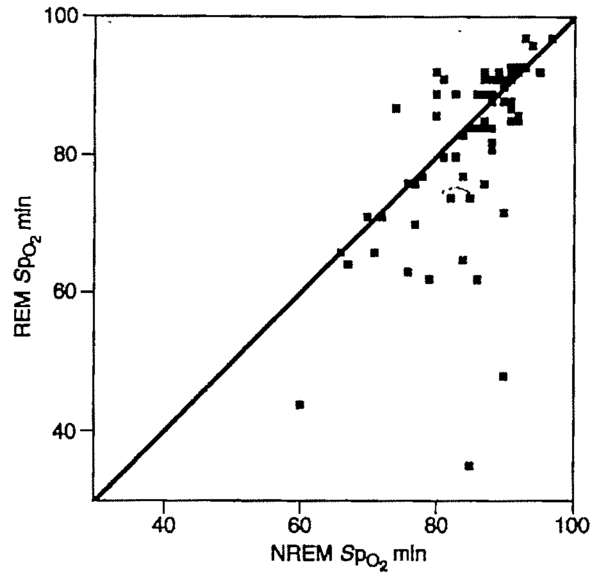

Fig 2 The minimum blood oxygen saturation (per cent) by pulse oximetry in REM plotted against the minimum saturation in NREM for each individual patient in the study. Those above the diagonal represent patients with a higher saturation nadir during REM and vice versa

Effect of age and body habitus

To determine if age or body habitus had any significant influence on sleep stage predominance, the REM values for both RDI and $Sp_{O_2,min}$ were subtracted from the corresponding NREM values, and the results plotted against both the age of the individuals and their body mass index (BMI). The plots are shown in Figs 3 and 4. Age had no discernible effect on sleep stage predominance in OSA with either RDI (slope=0.27, r^2=0.019) or $Sp_{O_2,min}$ (slope=0.015, r^2=0.000). With increasing BMI there would appear to be a slight trend towards REM predominance, more so for $Sp_{O_2,min}$ (slope=0.47, r^2=0.093) than RDI (slope=−1.12, r^2=0.083). At best, our data suggest that there is an increased likelihood of REM predominance in terms of minimum saturation only if the BMI is greater than 35 kg m^{-2}.

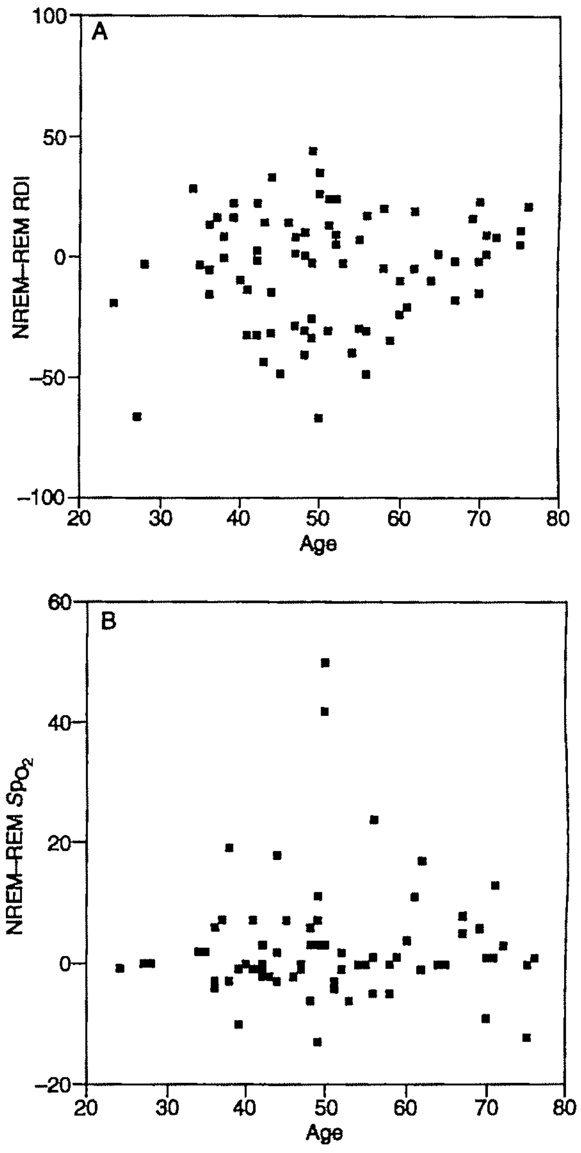

Fig 3 (A) The difference between the NREM and REM respiratory disturbance indices (events per hour) for each patient plotted against his/her age in years. (B) The difference between the NREM and REM saturation nadirs (per cent) for each patient plotted against his/her age in years.

Discussion

Major surgery is followed by a period of significant alteration in sleep architecture.[2 6–10] Most notably, REM, slow wave sleep (SWS – NREM sleep stages three and four) and total sleep time are variably reduced in the nights immediately following surgery, and there is a tendency for these to rebound for one or two nights thereafter.[2 8 9] Perhaps based on an assumption that sleep apnoea is worse during REM, some consider that REM rebound is likely to be associated with increased risk of late postoperative nocturnal hypoxaemia and consequently ischaemia-related complications.

There is some direct evidence to support this. Knill *et al.*[11] studied six obese patients undergoing gastroplasty and found, despite a substantially higher number of apnoeas and hypopnoeas in NREM, that there were more severe desaturations during REM postoperatively. However, the mean BMI of that series was more than 50 kg m^{-2} and our data concerning BMI could potentially explain a finding of REM predominance for desaturation. Rosenberg *et al.*[8] reported a similar finding for a series of 10 patients, but a number of issues may have affected their observations. The method of sleep monitoring (using a modified F3-A2 electro-encephalogram channel) and scoring (using 6-s instead of 30-s epochs) does not appear to have been standard. Airflow was not measured, so that the oximetry data are open to question with respect to artefact. The data are tabulated in a way that makes it difficult to assess, but it

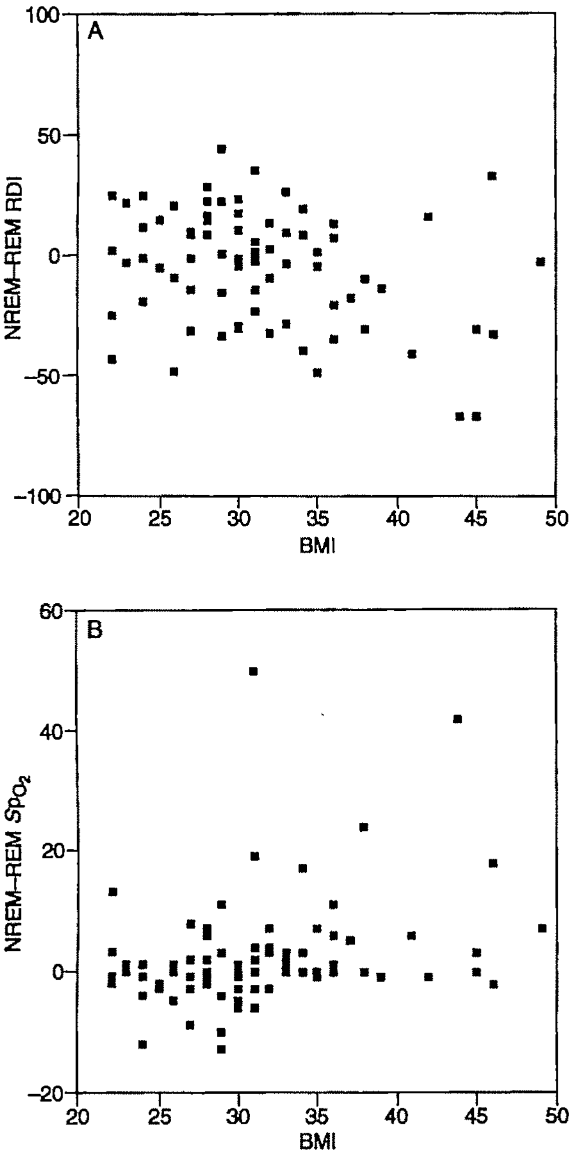

Fig 4 (A) The difference between the NREM and REM respiratory disturbance indices (events per hour) for each patient plotted against his/her body mass index (kg m^{-2}). (B) The difference between the NREM and REM saturation nadirs (per cent) for each patient plotted against his/her body mass index (kg m^{-2}).

appears that the greatest number of desaturations occurred during the night before the main REM rebound night, when there was less REM than preoperatively. It is also quite possible that their data were skewed by what appears to be a single patient with severe pre-existing sleep apnoea.

NREM/REM apnoea or desaturation differentials have been reported in only a few studies of OSA, often incidentally. Results similar to those in the current study have been reported.[12 13] Despite this, REM predominance of OSA seems to be a widely held assumption in the anaesthesia literature. Central sleep apnoea, on the other hand, is reported to be most common in NREM stages one and two[14] and actually reduced by REM sleep.[15] Less common than OSA, it is nevertheless prevalent in certain conditions, especially men with left ventricular dysfunction.[16–18] Even when congestive heart failure is stable and optimally treated, the incidence of CSA has been reported to be as high as 75% in this group.[19]

Direct extrapolation of results in a diagnostic sleep laboratory to the postoperative condition is not possible. Sleep architecture may be affected by a variety of factors in each situation and any effect this might have on stage predominance of apnoea would be a matter of speculation. The effect of concurrent illness is also not known, although it could be assumed that surgical patients would have a similar incidence and degree of respiratory disease to that of our patients.

Despite these potential limitations, our findings suggest that the effects of postoperative sleep disturbance on sleep and breathing may be more complex than previously thought.

Apnoeas tend to be longer during REM,[20 21] presumably as a consequence of reduced arousability.[22] In patients having a very large number of apnoeas, any increase in the apnoea duration will actually limit the time available for other apnoeas to occur, perhaps increasing the degree of desaturation and reducing the RDI during REM. This is consistent with our data (Figs 1 and 2).

Sleep stage may be important for other reasons. REM apnoeas are associated with a greater increase in arterial pressure than those occurring in NREM, although the difference was fairly modest.[23] While we were unable to control for body position in our analysis, others have demonstrated that sleep stage also determines the position dependency of obstructive apnoeas in some subjects.[20 24] Interestingly, position dependence seems to be a largely NREM phenomenon. Patients tend to be nursed supine after many surgical procedures, so an increase in the NREM/REM ratio of apnoeas might be expected postoperatively. This is supported by the findings of Rosenberg-Adamsen *et al.*[4] and would go against the assumption that REM rebound leads to greater risk. NREM supine apnoeic events may be an important factor in increasing apnoeic episodes in the early postoperative phase, before any period of REM rebound, consistent with the findings of Rosenberg *et al.*[8]

Conclusion

We have limited data on the role of sleep in the recovery of patients from surgery and anaesthesia. Most of the views expressed have been largely speculative. Although a REM rebound-related increase in apnoea is a possible cause of postoperative morbidity, our data from the sleep laboratory suggest that this assumption should be considered critically, and that more direct evidence from the postoperative ward is required. A small number of patients, mainly those with severe OSA, do appear to have a tendency to REM predominance of their apnoea. REM rebound might be more important to this group. Preoperative identification of such patients remains a major problem. The effects of sleep stage on factors other than upper airway patency also need to be determined.

Central apnoea and its sleep stage dependence has not been considered at all in the postoperative setting. Because CSA is common with patients suffering from cardiac dysfunction, a group already at increased perioperative risk, this disorder warrants further investigation. The reported NREM predominance of this form of sleep apnoea complicates the area of postoperative sleep disturbance considerably.

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Bispectral analysis of the electroencephalogram does not predict responsiveness to verbal command in patients emerging from xenon anaesthesia[†]

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The bispectral index (BIS) is derived empirically from the electroencephalogram database of patients receiving common anaesthetics, but it may not be valid for uncommon agents. Therefore, we investigated how xenon affects the BIS. Nine and 11 patients were anaesthetized with 0.8 of the minimal alveolar concentration (MAC) of isoflurane (0.92%) and xenon (56%), respectively. After the end of operation, these concentrations were decreased in decrements of 0.1 MAC (isoflurane 0.12% or xenon 7%) and each new concentration was maintained for 15 min. This was repeated until the patient first opened her eyes or squeezed the investigator's hand on command. Isoflurane and xenon at 0.8 MAC reduced the BIS to a median of 40 (range 36–53) and 36 (30–61), respectively. With decreasing concentrations of isoflurane, the BIS increased progressively and it reached a median of 96 (90–98) when the patients awoke. In contrast, four patients receiving xenon responded to verbal command while the BIS was below 50 [median 45 (range 41–49)]. The remaining seven patients in the xenon group awoke when their BIS was greater than 80 [median 96 (range 82–98)], but in four of them the BIS was no greater than 50 when the xenon concentration was only 0.1 MAC (7%) higher than that associated with awakening. We conclude that low BIS values (<50) do not guarantee adequate hypnosis during xenon anaesthesia.

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The bispectral index (BIS) is an electroencephalogram (EEG)-derived univariate scale reflecting the level of hypnosis in anaesthetized patients.[1] Because the algorithm to compute the BIS was formulated empirically on the basis of the EEG data of patients receiving common anaesthetics such as isoflurane and propofol,[1] the BIS may not necessarily be valid for other agents. For example, ketamine does not affect the BIS value when administered at doses that produce unconsciousness.[2,3]

Xenon is an inert gas with many favourable characteristics as an anaesthetic,[4] including a low blood/gas partition coefficient (0.12),[5] a minimal alveolar concentration (MAC; 71%)[6] that is lower than that of nitrous oxide but analgesic properties similar to those of nitrous oxide,[7,8] a lack of toxicity, and harmlessness to the environment. However, xenon was not considered when the algorithm for the BIS was formulated, and whether the BIS appropriately reflects the depth of anaesthesia produced by this gas has not been investigated. Therefore, we performed a randomized prospective study to characterize how the BIS changes as the concentration of xenon is decreased during emergence from anaesthesia until the patient awakens and regains responsiveness to verbal command.

Patients and methods

Written consent to participation in the study was obtained from 20 women of ASA physical status I or II, who were

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aged 38–56 yr and were scheduled for elective total abdominal or vaginal hysterectomy. The women were studied according to a protocol approved by the Institutional Human Studies Committee of Teikyo University. Exclusion criteria included a history or the presence of neurological diseases, ingestion of medications known to influence anaesthetic or analgesic requirements, and contraindications to extradural anaesthesia.

The unpremedicated patients had an extradural catheter placed at the L2/3 interspace, and after a 3 ml test dose, 10 ml of mepivacaine 1.5% with 1:200 000 epinephrine was administered. If the sensory level of T10 or higher to pinpricks was not obtained within 15 min, the extradural catheter was judged to be functioning inadequately and the patient was not included in the study.

In addition to routine monitoring devices, the EEG signal was acquired using four electrodes (Zipprep™; Aspect Medical Systems, Natick, MA, USA) applied to the forehead, with one on each outer malar bone, one at the centre of the forehead and one (ground) on either side of the centre electrode. The BIS (version 3.22) value and the 95% spectral edge frequency (SEF_{95}) were displayed using an Aspect EEG monitor (Model A-1050; Aspect Medical Systems) and were stored every 5 s on a personal computer for later off-line analysis throughout the study.

The patients were assigned randomly to receive either xenon (n=11) or isoflurane (n=9) for maintenance of anaesthesia. After a stable baseline EEG had been obtained with the patients' eyes closed, those who were to receive xenon and isoflurane received propofol 2.5 mg kg^{-1} intravenously (i.v.) and an inhalation of 5% sevoflurane, respectively, for induction of anaesthesia. The larynx and upper trachea were sprayed with 4% lidocaine 3 ml, and the trachea was then intubated with the aid of vecuronium 10 mg i.v. In the xenon group, anaesthesia was maintained with 56% xenon (0.8 MAC) in oxygen using a closed breathing system (all concentrations of inhalational anaesthetics are end-tidal). The isoflurane group received isoflurane 1.0–1.5% in a 6 litre min^{-1} flow of oxygen, which was reduced to 0.92% (0.8 MAC) at least 15 min before the end of surgery. All patients also received a continuous extradural infusion of 1.5% mepivacaine containing 1:200 000 epinephrine at 6–8 ml h^{-1} to maintain the mean arterial pressure and heart rate within 20% of the preoperative values. The lungs were ventilated mechanically to maintain the end-tidal concentration of carbon dioxide (CO_2) at 30–35 mm Hg, and additional doses of vecuronium were administered if clinically indicated. The body temperature, measured with an oesophageal sensor, was maintained by the use of a warming mattress placed on the operating table. Intravenous fluids were also warmed.

The end-tidal concentration of xenon was monitored continuously using a xenon analyser (Anzai Medical, Tokyo, Japan), the effective working range of which was 1–100% with error <1% and 90% response time less than 1 s. This device measures absorption by the gas mixture of a characteristic x-ray, which is proportional to the concentration of xenon in the gas mixture. The end-tidal concentrations of carbon dioxide and isoflurane were measured using an infrared analyser (Capnomac Ultima; Datex, Helsinki, Finland). In the xenon group, an in-line infrared capnogram (Hewlett-Packard, Waltham, MA, USA) was used instead. These analysers were calibrated before each use according to the manufacturers' instructions.

Shortly before the end of surgery, residual neuromuscular blockade was reversed with neostigmine 2.5 mg and atropine 1.0 mg i.v. and recovery was verified by the train-of-four response to ulnar nerve stimulation. When surgery was complete, a designated investigator, blinded both to the anaesthetic administered and to the EEG data, asked the patient in a normal tone to open her eyes and to squeeze and release the investigator's hand. If the patient failed to follow both of these commands, the end-tidal concentration of xenon or isoflurane was reduced by 7 or 0.12%, respectively (both approximately 0.1 MAC). The new concentration was maintained for 15 min. During this period, the patient's ability to respond to verbal commands was checked every 5 min and whenever clinical signs of imminent awakening, such as coughing, bucking and frowning, were noted. If no response was observed for the entire 15 min period, the concentration of anaesthetic was reduced again. This process was repeated until an alveolar concentration was reached at which the patient responded appropriately to either one of the commands. This concentration was termed the awakening concentration. Care was taken to minimize stimuli other than verbal commands during the entire wake-up period. Mechanical ventilation was continued during the entire period. When coughing or bucking hindered effective ventilation with positive pressure, the patient was allowed to breathe spontaneously.

The BIS and SEF_{95} values at each concentration at which no response to verbal command was observed during the entire 15-min equilibration period were calculated by averaging the values obtained over the last 3 min of that period. At the awakening concentration, the values displayed at the time of the patient's response were recorded. The data from right- and left-sided electrodes were averaged.

Fifteen minutes after tracheal extubation, the extradural block level to pinpricks was examined, and the patient was asked to rate her incisional pain using a verbal rating scale of 0–10, values of 0 and 10 representing no pain and the worst pain imaginable, respectively. All patients were asked 2 h after the operation if they remembered being called by their name when they woke up.

The BIS values, the postoperative pain ratings and the extradural analgesia levels are reported as median (range) and were analysed using Mann-Whitney U-tests. Other data are presented as mean (SD) and were analysed using unpaired t-tests. A P value less than 0.05 was considered statistically significant.

Results

The two anaesthetic treatment groups were comparable with respect to the patients' characteristics, the BIS and SEF_{95} values recorded before induction of anaesthesia, and the postoperative data listed in Table 1.

The 0.8 MAC concentrations of isoflurane and xenon reduced the BIS to 40 (36–53) and 36 (30–61) and the SEF_{95} to 13.6 (2.2) and 8.3 (4.2) Hz, respectively (Figs 1 and 2). The BIS did not differ between the groups, whereas the SEF_{95} was significantly lower with xenon.

The patients who received isoflurane and xenon awoke at the end-tidal concentrations of 0.36 (0.06) and 31 (7)%, respectively. Those who received isoflurane demonstrated progressively increasing BIS and SEF_{95} as the anaesthetic concentration was decreased (Figs 1 and 2, upper panel). On awakening, these values were 96 (90–98) and 25.1 (2.3) Hz, respectively.

Xenon was markedly different from isoflurane in the BIS value on awakening. Four patients in the xenon group awoke while their BIS values were less than 50 (45 (41–49)) and had not appreciably increased from those observed at higher concentrations of xenon (Fig. 1, lower panel). The remaining seven patients awoke with the BIS greater than 80 (96 (82–98)), but in four of them the BIS value was no greater than 50 when the concentration of xenon was only 0.1 MAC (7%) higher than the awakening concentration (Fig. 1, lower panel).

The SEF_{95} values of the xenon group changed similarly to the BIS (Fig. 2, lower panel). Thus, all four patients who awoke with their BIS below 50 and one who did so at a BIS of 82 showed relatively low SEF_{95} values on awakening (11.1 (2.9) Hz, range 6.7–14.0 Hz). On the other hand, the remaining six patients awoke at a SEF_{95} value of 25.0 (3.2) Hz, but in three of them the SEF_{95} value was relatively low (<12 Hz) when the xenon concentration was only 0.1 MAC higher than that associated with awakening.

No subject experienced major anaesthesia-related adverse events. When interviewed postoperatively, none of the four patients who awoke with the BIS below 50 remembered that they were called by their name when they were waking up, while two of the seven patients who awoke with the BIS greater than 80 remembered it vaguely.

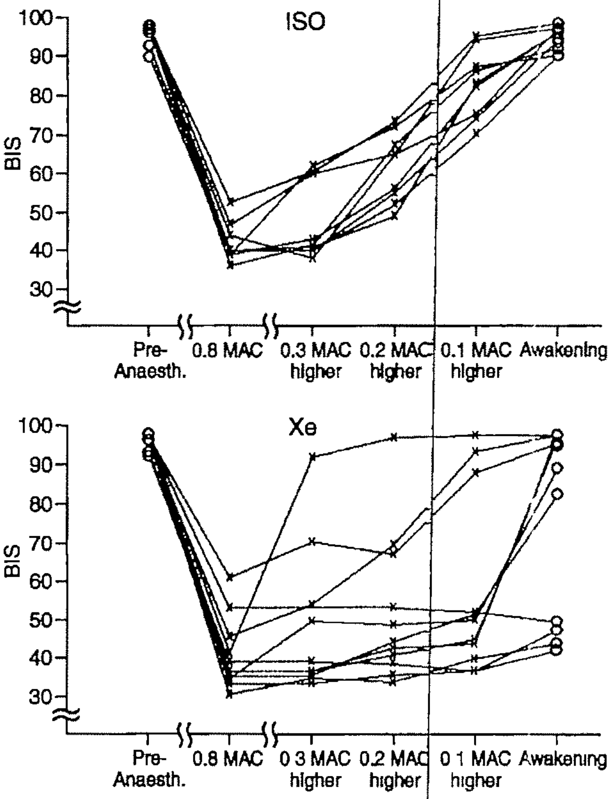

Fig 1 Changes in the BIS values in each patient with decreasing concentrations of isoflurane (*upper panel*) or xenon (*lower panel*) until they demonstrated the first response to verbal command (awakening) The symbols X and O indicate the absence and presence of response to verbal command, respectively Pairs of symbols connected by the broken lines were recorded at the same absolute concentration of xenon This was because, depending on the awakening concentration for each individual, the 0 2 or 0.3 MAC higher concentrations of xenon were equal to 0.8 MAC

Table 1 Patient characteristics and postoperative data The extradural dose is the total volume of 1 5% mepivacaine with 1 200 000 epinephrine administered extradurally until 15 min after removal of the tracheal tube The extradural level was checked using pinpricks 15 min after removal of the tracheal tube. The pain rating was the numerical quantification of incisional pain by the patient using a verbal rating scale of 0–10, 0 and 10 representing no pain and the worst pain imaginable, respectively Data are mean (SD) except for the BIS values, the extradural level and the pain rating, which are median (range)

Patient characteristics and postoperative data	Xenon	Isoflurane
Age (yr)	47 (5)	46 (4)
Height (cm)	156 (3)	156 (5)
Weight (kg)	54 (6)	59 (7)
Preinduction BIS	98 (93–98)	98 (90–98)
Preinduction SEF_{95} (Hz)	18.6 (5 0)	19 9 (3 9)
Duration of anaesthesia (min)	115 (39)	121 (34)
Oesophageal temperature (°C)	36.0 (0 1)	35 9 (0.2)
Extradural dose (ml)	28 (4)	29 (6)
Extradural level	T7 (T4–T11)	T9 (T6–T11)
Pain rating	2 (0–3)	2 (0–4)

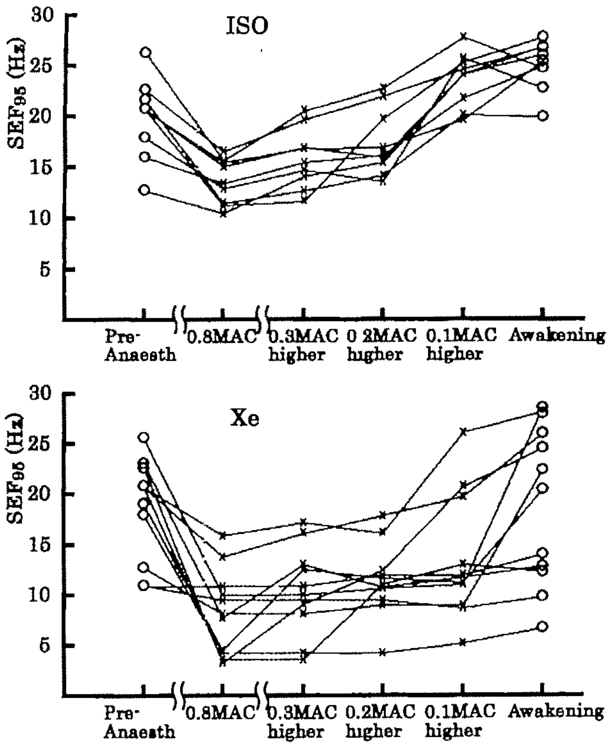

Fig 2 Changes in SEF_{95} values in each patient with decreasing concentrations of isoflurane (*upper panel*) or xenon (*lower panel*) until they demonstrated the first response to verbal command (awakening). The figures were drawn using specifications identical to those for Fig. 1

Discussion

Our results for isoflurane are consistent with the well-documented reliability of the BIS as an indicator of the depth of anaesthesia.[9] However, this is not the case for xenon. Most remarkably, 37% (4/11) of the patients responded to verbal command when their BIS value was lower than 50, which would normally indicate deep hypnosis.[10] In addition, among the remaining seven patients who awoke with their BIS greater than 80, four had BIS values no greater than 50 when the concentration of xenon was only 0.1 MAC (7%) higher than that associated with awakening. Therefore, we conclude that those who are anaesthetized with xenon can be awake or in the near-awakening state even when their BIS values are no greater than 50.

Two issues need to be addressed when considering the validity of our data. First, one may argue that the behaviours we used as the end-point of awakening (eye-opening and hand-squeezing) were too simple to distinguish a non-specific or reflexive reaction to hearing a voice from a conscious and deliberate response to the command. However, a recent investigation[11] that evaluated the level of hypnosis using graded and varied stimuli and multiple verbal commands demonstrated that the participants either responded fully to all the stimuli and commands or showed no responses at all. Intermediate levels of responsiveness were observed rarely. This strongly suggests that a positive response to a simple verbal command is sufficient evidence that the subject is awake.

The second issue involves a computational delay of the BIS monitor device. The BIS value reported by the monitor represents an average value derived from the previous 60 s of usable EEG data.[1] Therefore, it is possible that the patients whose BIS values on awakening were less than 50 had experienced an increase in the BIS within the 60 s preceding awakening and that their BIS values at the exact moment of awakening were actually greater than 50. However, we believe this is unlikely because we provided a quasi-stable level of anaesthesia for 60 s preceding the moment of awakening by maintaining the end-tidal concentration of xenon constant, except for stepwise reductions at every 15 min, and by leaving the patients undisturbed as much as possible. Moreover, even if this increase actually occurred, this does not invalidate our conclusion that the low BIS may be associated with the near-awakening state during xenon anaesthesia, because the BIS stayed low until less than 60 s before awakening.

We can speculate how a level of xenon anaesthesia sufficiently light to permit a response to verbal command was associated with a BIS less than 50 in some patients, as the BIS computation algorithm has not been published. Our results demonstrated that, when the xenon patients awoke while their BIS were less than 50, their EEGs were always slowed, as indicated by the SEF_{95} values of no greater than 14 Hz. In marked contrast, isoflurane permitted our patients to awaken only after their SEF_{95} had increased to above 20 Hz. Because the BIS generally decreases as the power of the EEG high-frequency components declines,[1] it is not surprising that the patients who awoke with low SEF_{95} also had low BIS values.

This study has several limitations. First, we used extradural analgesia, which may affect the sensitivity of the brain to general anaesthetics.[12] Whether it disturbs the relationship between the BIS and the clinical level of hypnosis is unknown. Secondly, we studied only females, although the relationship between the dose of anaesthetics and the BIS may be sex-dependent.[13] Thirdly, we studied only one end-point of hypnosis, i.e. the presence or absence of responses to verbal command, although other endpoints, especially memory formation, are also clinically relevant. It is reassuring that the four patients of the xenon group who awoke with BIS below 50 did not recall that they had been called by their names when waking up. However, the number of the patients studied was too small to draw any firm conclusion about whether low BIS values guarantee loss of memory formation during xenon anaesthesia.

In summary, we have demonstrated that BIS values less than 50 do not guarantee adequate hypnosis during xenon anaesthesia. Therefore, other modalities for monitoring the hypnotic level are required if xenon is to be used in clinical practice.

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Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults[†]

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Desflurane is not used for the induction of anaesthesia despite its favourable pharmacokinetic characteristics because it causes airway irritation. We investigated whether pretreatment with i.v. narcotics reduced unwanted effects. One hundred and eighty adults were randomized to three groups (60 per group) to receive i.v. saline, fentanyl 1 μg kg^{-1} and morphine 0.1 mg kg^{-1}, respectively, before inhalational induction with desflurane in nitrous oxide and oxygen. Mean time to loss of response to commands was 4.0 min, without significant differences between groups. The incidence of coughing was greater (25%) in the control group than in the fentanyl (5.0%) and morphine groups (8.3%). The incidence of apnoea was 20.0% in the control group versus 13.3 and 5.0% in the fentanyl and morphine groups, respectively. Laryngospasm developed in 11.7% of controls compared with 3.3 and 1.7% in the fentanyl and morphine groups, respectively. More patients in the control group had excitatory movements (46.7%) than in the fentanyl (16.7%) and morphine (8.3%) groups. These results demonstrate that i.v. opioids reduce airway irritability significantly during inhalational induction with desflurane in adults.

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Keywords: anaesthetics, volatile, desflurane; anaesthetics i.v., opioid, morphine; anaesthetic techniques, induction; airway

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Desflurane is a halogenated ether with low solubility (partition coefficients: blood:gas, 0.42; oil:gas, 18.7[1]), giving rapid induction and emergence from anaesthesia.[2–3] It has other valuable features, such as stability in soda lime[4–5] and negligible biotransformation to toxic metabolites,[6–7] and hence a low potential for hepatic and renal toxicity. However, it can cause airway irritation when used for the induction of anaesthesia in adults[8–12] and children, leading to coughing, apnoea, laryngospasm, copious secretions and excitatory movements.[13 14] We studied the ability of intravenous opioids to reduce the airway irritation caused by desflurane.

Patients

With hospital ethics committee approval and patient consent, 180 adult ASA I and II patients aged between 18 and 65 yr who were scheduled for elective surgery entered the study. The exclusion criteria were anaemia, a history suggestive of malignant hyperthermia, a family history of anaesthetic mishaps, severe lung disease, chronic cough (cough occurring for at least 3 months of the year for 2 successive years), obesity (body mass index >30 kg m^{-2}), previous exposure to desflurane, smoking, and medication that could interfere with the study (e.g. anxiolytics). Patients with a history of upper respiratory tract infection within 1 month of surgery were also excluded. Patients were randomized to three groups (60 patients per group) to receive morphine, fentanyl or saline before induction with desflurane. Randomization was by means of sealed envelope.

Methods

Monitoring included continuous ECG, pulse oximetry, non-invasive blood pressure, end-tidal CO_2 and expired desflurane concentration (Hewlett-Packard Anaesthetic Gas Module M1026A).

The opioids were given from a syringe containing either fentanyl, morphine or saline made up to 10 ml (in saline if necessary), prepared by an assistant who was not involved

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[†] The abstract was presented in poster form at the annual meeting of the American Society of Anesthesiologists, Dallas, Texas, October 1999, and was published in *Anesthesiology* 1999; 91. A431.

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Table 1 Characteristics of the three groups

	Control	Fentanyl	Morphine
Number	60	60	60
Age (yr) (mean) (range)	43(21–65)	45(22–65)	46(17–65)
Weight (kg) (mean (SD))	56 (10)	55 (9.6)	58 (13 2)
ASA status (I, II)	52, 8	56, 4	50, 10
Sex (M, F)	25, 35	19, 41	23, 37

Table 2 Time required for induction and the expired desflurane concentration at induction. Values with the same superscript are significantly different ($P<0.05$)

	Control	Fentanyl	Morphine
Time to loss of response to command (min)Mean (SD)Median	4.0 (1 1)4 0	3.8 (1 4)3 1	4 0 (1.5)3.4
Expired desflurane concentration at loss of response to command (%)Mean (SD)Median	3.8 (1.1)^{a}3.6	3.9 (1 2)^{b}3.8	4 4 (1 5)^{a,b}4 1

Table 3 Incidence of cough, apnoea, laryngospasm and excitatory movements during desflurane induction. Values with the same superscript are significantly different ($P<0$ 05)

	Control	Fentanyl	Morphine
Cough	25.0%^{a,b}	5.0%^{a}	8.3%^{b}
Apnoea	20.0%^{c}	13.3%	5 0%^{c}
Excitatory movements	46 7%^{d}	16.7%	8 3%^{d}
Laryngospasm	11.7%^{e}	3 3%	1.7%^{c}

in the study. The anaesthetist administered the drugs over 1 min and was not aware of the contents of the syringe.

Saline (group C), morphine 0.1 mg kg^{-1} (group M) or fentanyl 1 μg kg^{-1} (group F) was given 2 min before preoxygenation with 100% oxygen at 6 litre min^{-1} for 3 min using a circle system with soda lime absorber. The oxygen flow was then reduced to 3 litre min^{-1} and nitrous oxide (50%) was started at 3 litre min^{-1}. Desflurane 1% was started and increased by 1% after every six breaths. Every 10 s during this period, each patient was asked to open his or her eyes. The time when the patient failed to respond to this command was taken as the time of completion of inhalational induction.

We recorded the age, sex, weight, ASA status, diagnosis and the type of surgical procedure for each patient. The reading of the pulse oximeter before induction and the lowest reading obtained during induction were noted. The time between starting desflurane and loss of consciousness was calculated and the expired desflurane concentration at loss of consciousness was noted. Any coughing, apnoea, laryngospasm or excitatory movements were noted. Coughing was considered mild if there were 1–3 coughs, moderate if there were 4–7 coughs and severe if there were 8 coughs or more. Apnoea was noted as no breathing movements for more than 30 s.

If patients developed laryngospasm, i.v. propofol 2 mg kg^{-1} was given with the addition of i.v. suxamethonium 1 mg kg^{-1} if necessary. The patients were then ventilated using the mask with 100% O_2 until saturation improved.

If apnoea and oxygen desaturation were present (Sp_{O_2} <90%, or a decrease of more than 5% from initial value), the lungs were ventilated via a mask until spontaneous respiration returned.

Statistics

Analysis of variance (ANOVA) was used to analyse parametric data and all non-parametric data were analysed using the Kruskal–Wallis and Mann–Whitney tests. A P value of <0.05 was considered significant.

Results

The three groups were comparable in age, sex, weight and ASA status (Table 1).

The induction times for the three study groups are given in Table 2, and were not significantly different (P=0.26).

The expired desflurane concentrations at loss of response to command are given in Table 2. The concentration was greater in the morphine group than in the control group (P=0.02).

The incidence of complications is shown in Table 3. Significant differences in coughing were found between the control and fentanyl groups (P=0.002) and between the

Table 4 Arterial pressure (mm Hg, mean (SD)) and heart rate (beats min^{-1}) before and after induction

	Control		**Fentanyl**		**Morphine**	
	Before	**After**	**Before**	**After**	**Before**	**After**
Systolic arterial pressure	133 (20.6)	131 (19.4)	134 (21.3)	131 (23.7)	140 (21.6)	131 (28.9)
Diastolic arterial pressure	71 (10.3)	73 (12.8)	70 (12.0)	67 (14.6)	75 (12.4)	73 (14.0)
Mean arterial pressure	92 (11.3)	91 (11.0)	91 (13.4)	90 (16.5)	99 (12.3)	95 (12.8)
Heart rate	72 (15.2)	78 (15.8)	73 (13.3)	64 (12.7)	80 (16.1)	69 (11.6)

control and morphine groups (P=0.013). No differences were found between the morphine and fentanyl groups.

The difference in apnoea between the control and morphine groups was statistically significant (P=0.012). No significant differences were found between the control and fentanyl groups or the morphine and fentanyl groups.

Seven patients in the control group had laryngospasm. In one of these, oxygen saturation decreased to 70%. Two patients in the fentanyl group and one patient in the morphine group had laryngospasm without oxygen desaturation. There was a significant difference between the control and morphine groups (P=0.025). No differences were found between the control and fentanyl groups or the morphine and fentanyl groups.

There were more excitatory movements in the control group than in the morphine group (P=0.025), but the control and fentanyl groups and the morphine and fentanyl groups did not differ.

The blood pressure and heart rate changes in the three groups are given in Table 4. Overall there were no group differences and the magnitudes of the changes were not of clinical significance.

Discussion

Expired desflurane concentration at the end of induction

The mean (SD) expired desflurane concentration at completion of induction in the control, fentanyl and morphine groups was 3.8 (1.1), 3.9 (1.2) and 4.4 (1.5)%, respectively. During the study, 50% N_2O was introduced together with desflurane. This could explain the lower expired desflurane concentration at the completion of induction, as the use of N_2O reduces the minimal alveolar concentration (MAC) of volatile anaesthetic.

This study showed a significant difference in the expired desflurane concentration at the end of induction between the control and morphine groups. This difference may have been the result of sedation cause by morphine.

No differences were found between the fentanyl and control groups. Fentanyl had a peak effect at 4–5 min. It may be that the effect of fentanyl was beginning to wear off (even though its duration of action is 20–30 min).

Time to loss of response to command

No differences were found between the three groups in the time taken to induction, which was approximately 5 min. This could be due to the slow, small increments in inhaled concentration in the study design because of the risk of laryngospasm.

Coughing occurs in 26–59% of patients during desflurane inhalation.[8–12] This is supported by our results. The control group had an incidence of coughing of 25.0%. Among the 14 patients who coughed, cough was mild in two, moderate in seven and severe in five. Morphine or fentanyl reduced the incidence of coughing. In the fentanyl group, all three patients had mild cough, whereas of the five patients who received morphine two had mild cough, two had moderate cough and one had severe cough.

Sevoflurane is often used for inhalational induction in both adults and children, with coughing in 16%.[17–19] The tidal volume induction technique may be associated with a greater incidence of airway complications compared with vital capacity induction.[17–19] Pretreatment with morphine or fentanyl reduces the incidence of airway complications below 10% during tidal volume induction using desflurane.

This study also supports the incidence of apnoea reported in the literature (13–35%),[8–12] with 20% in the control group. Pretreatment with morphine or fentanyl reduced the incidence of this adverse effect to 5 and 13.3%, respectively. These incidences are comparable with those reported for sevoflurane (16%).[17–19]

The incidence of excitation is reported to be 24–43%,[8–12] and was 47% in this study. Pretreatment with morphine or fentanyl reduces the incidence to 8.3% and 16.7%, respectively. When sevoflurane is used for induction 12% of patients exhibit excitatory movements.[17–19] Morphine pretreatment reduces the incidence of excitatory movements to a comparable figure during desflurane inhalational induction.

Seven patients (11.7%) in the control group had laryngospasm during induction, similar to the reported incidence of up to 17%.[8–12] Three of these seven patients also had cough of moderate severity, two had apnoea and five had excitatory movements. One patient, a 31-yr-old ASA I man, had significant desaturation during induction. He also had excitatory movement but he did not cough or become apnoeic during induction. His blood pressure remained stable.

One patient in the morphine group had laryngospasm. He did not cough or have apnoea or excitatory movements during induction, or show arterial desaturation during the episode. Two patients in the fentanyl group had laryngospasm with mild cough and excitatory movement. They did not have apnoea or arterial oxygen desaturation during this episode. Laryngospasm is reported in 3–8% of patients induced with sevoflurane and a tidal volume induction technique.[18] [19] Pretreatment with morphine or fentanyl reduces the incidence of laryngospasm during desflurane induction to a figure comparable with sevoflurane induction.

Conclusion

Pretreatment with morphine or fentanyl reduces the incidence of airway irritation to a value similar to that value reported with sevoflurane during inhalational induction of anaesthesia. However, for direct comparison a randomized study should be performed. With opioid pretreatment, desflurane can be considered for inhalational induction of anaesthesia in adults.

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Nodal rhythm and bradycardia during inhalation induction with sevoflurane in infants: a comparison of incremental and high-concentration techniques

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We studied heart rate and rhythm changes during sevoflurane inhalation induction in 60 healthy, unpremedicated infants. Patients were allocated randomly to receive an incremental (2% sevoflurane, increased every four to six breaths by 2% increments, to 8%) or high-concentration induction technique (8% sevoflurane from the outset). The ECG was recorded for 330 s (30 s pre- and 300 s postinduction) using a mini-Holter device (Recollect Dual Channel, Hertford Medical) and later analysed by an independent observer. Twelve patients developed nodal rhythm (six in each group), but no other dysrhythmias were recorded. The onset of nodal rhythm was associated with bradycardia (<80 bpm) in seven out of 12 cases, and occurred significantly earlier in the high-concentration group (median 123 (range 99–139) s versus 164 (127–238) s). Its duration was similar in both groups (62 (2–84) s versus 90 (20–167) s). These findings highlight the importance of using continuous ECG analysis when studying volatile anaesthetic agents in young children.

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Sevoflurane is frequently used for inhalation induction of anaesthesia in children, with little evidence of cardiovascular side effects.[1 2] Recent reports, however, suggest that some children may experience significant bradycardia or cardiac conduction abnormalities.[3 4] The aim of this study was to investigate heart rate and rhythm changes during inhalation induction of anaesthesia with sevoflurane in infants using either incremental or high-concentration techniques.

Patients and methods

With local research ethics committee approval and parental consent, we recruited 60 healthy, unpremedicated infants, aged 6 weeks to 20 months presenting for elective surgery. We excluded children with known cardiac and respiratory disease, and those on medications known to affect cardiac conduction. Subjects were allocated randomly to receive either incremental or high-concentration sevoflurane using a computer-generated random number allocation and closed-envelope technique. Anaesthesia was induced in the anaesthetic room with the child either cradled on a parent's lap or supine on an anaesthetic trolley. Electrocardiograph (ECG) monitoring was commenced before induction using a mini-Holter device (Recollect Dual Channel, Hertford Medical). This is a programmable and portable system that uses four electrodes to monitor the bipolar lead CM5 for a period of up to 45 min with dual channel recording. Data are recorded on 1 megabyte of removable RAM which can then be downloaded and analysed further using the accompanying computer software. We programmed the Recollect device to record the ECG for 30 s pre- and 300 s postinduction. All patients were monitored with pulse oximetry. We did not attempt to record systemic arterial pressure during induction because we did not want the stimulus of an inflating cuff to influence measurement of heart rate.

In the incremental group (group I), 2% sevoflurane was introduced via a well-fitting face mask in 33% oxygen in nitrous oxide (total flow 6 litres min^{-1}) through a Jackson-Rees modification of the Ayre's T-piece. The sevoflurane concentration was increased by 2% every four–six breaths up to a maximum of 8%. In the high-concentration group

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Table 1 Patient characteristics (mean (SD))

	Group I (n=29)	Group H (n=31)
Sex (M/F)	(19/10)	(26/5)
Age (months)	8.6 (5.4)	7.3 (4.8)
Weight (kg)	8.1 (2.1)	7.8 (3.1)

Table 2 Pre-induction, minimum and maximum heart rate (mean (SD))

	Group I (n=28)	Group H (n=31)
Pre-induction (bpm)	145.8 (25.8)	155.5 (24.8)
Minimum (bpm)	103.9 (18.7)	101.4 (17.0)
Maximum (bpm)	173.1 (26.8)	169.6 (16.6)

(group H), the anaesthetic circuit was primed with 8% sevoflurane in 33% oxygen in nitrous oxide before induction. After loss of eyelash reflex, the sevoflurane concentration was decreased to 5% until depth of anaesthesia was judged sufficient to allow i.v. cannulation. At the end of the study period, Holter monitoring was stopped and replaced by conventional three-lead ECG and non-invasive arterial pressure monitoring. Airway complications and arterial haemoglobin oxygen saturation (Sp_{O_2}) below 95% were noted.

Pre- and postinduction ECG recordings were analysed for changes in heart rate and rhythm by an observer blinded to the method of induction. Bradycardia was defined as a heart rate of <80 bpm. Nodal rhythm was identified when the P wave closely preceded, occurred within, or followed the QRS complex. Data were analysed using Student's *t*-test and the Mann–Whitney test, and presented as mean (SD) or median (range) as appropriate. The sample size required to detect a difference of 20 bpm in heart rate between the two groups was calculated at 48 (power of 0.8) and 65 (power of 0.9) based on results from a pilot study. A *P*-value of <0.05 was taken to be statistically significant.

Results

A total of 60 infants were enrolled in the study: 29 in group I and 31 in group H. The two groups were comparable in age, sex and weight (Table 1), and type of surgical procedure. In each group there were 17 general and three orthopaedic surgical procedures. Plastic and other peripheral surgical procedures accounted for nine cases in group I, and 11 cases in group H. One patient was withdrawn from group I due to technical difficulties resulting in the loss of the ECG recording. This patient was excluded from further analysis.

Pre-induction, and minimum and maximum heart rate during induction did not differ between the groups (Table 2). There were no pre-existing cardiac conduction abnormalities detected, and pre-induction heart rates were in line with previously documented resting heart rates in awake infants.[5] The majority of patients remained in sinus rhythm throughout. However, six patients in each group developed a nodal rhythm. An example of the onset of nodal rhythm is shown in Fig. 1. This subgroup of 12 patients was comparable in age to the study population (8.3 (4.2) months versus 7.8 (5.3) months, respectively). There was a significant difference in onset time of nodal rhythm between the groups with onset being earlier in group H 123 (99–139) s versus 164 (127–238) s in group I (Fig. 2). The duration of nodal rhythm was similar in both groups: 62 (2–84) s in group I and 90 (20–167) s in group H (P=0.179). The change in rhythm was associated with bradycardia in seven of the 12 cases (three in group I and four in group H). Of the 47 patients who remained in sinus rhythm throughout induction, only one patient had a decrease in heart rate to less than 80 bpm. There were no other ventricular or supraventricular dysrhythmias recorded during the study period.

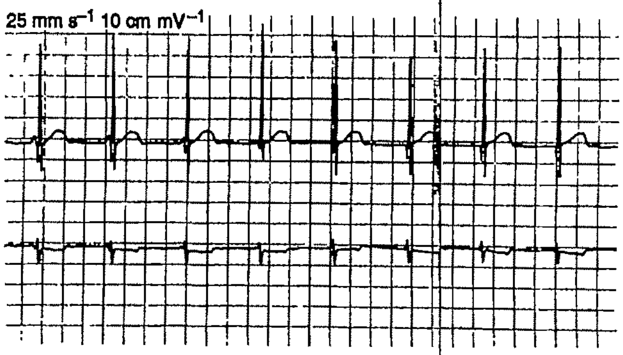

Fig 1 An example of onset of nodal rhythm during sevoflurane induction in an infant.

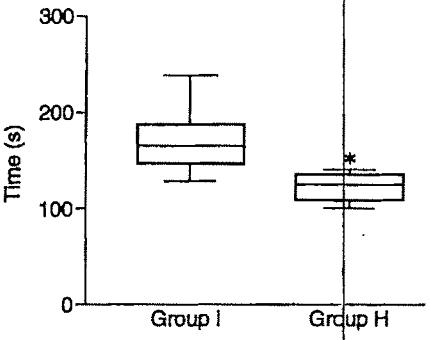

Fig 2 Onset time of nodal rhythm in incremental group (I) and high-concentration group (H). Box and whisker plots show median, 25th and 75th centiles, and range (*P=0.015).

Three patients had an episode of arterial haemoglobin oxygen desaturation (Sp_{O_2} <95%) during induction, but none of these was associated with heart rate or rhythm changes.

Discussion

Under the study conditions described, detailed analysis of the ECG recorded during inhalation induction of anaesthesia with sevoflurane in healthy unpremedicated infants demonstrated a 20% incidence of nodal rhythm irrespective of inhalation technique. This finding surprised us because previous studies of inhalation induction of anaesthesia with sevoflurane in young children have not highlighted rhythm disturbance. In a comparison of rapid (8%) sevoflurane induction with 5% halothane in young children (aged 3 months to 3 yr), conduction abnormalities were not a significant problem.[6] It is noteworthy, however, that both groups were premedicated with atropine. Under conditions where a deep level of inhalation anaesthesia is required for relatively short duration, such as paediatric bronchoscopy, nodal rhythm may occur with sevoflurane, although the incidence of this and other dysrhythmias is much less than when using halothane.[2]

In our study, the onset of nodal rhythm was significantly earlier in the high-concentration group, but the duration was similar in both groups. This may be because the development of nodal rhythm is related to depth of anaesthesia. In addition, immaturity of the autonomic nervous system in infants makes this group particularly susceptible to the effects of volatile anaesthetic agents on cardiac conduction pathways. The failure of previous studies to document conduction abnormalities may reflect the method of ECG recording utilized. The poor quality of some single lead (lead II) rhythm strip recordings may not enable accurate analysis. In a comparison of the incidence and nature of arrhythmias using halothane or sevoflurane in paediatric dental anaesthesia,[7] Holter monitoring detected a high incidence of arrhythmias (48% versus 16%). Despite simultaneous conventional ECG monitoring, some of these were undetected by the anaesthetist (personal communication). In clinical studies of inhalation agents in children, the precise method of ECG analysis is often not clarified.

A potential criticism of our study is that systemic arterial pressure was not recorded during induction. However, the clinical usefulness of non-invasive arterial pressure measurement during an inhalation induction of anaesthesia in infants is limited, and the validity of intermittent measurements during a dysrhythmia is questionable. Invasive arterial pressure monitoring could not be justified in this study population. Once the induction and ECG recording phases were complete, non-invasive arterial pressure and other monitoring commenced in the usual manner, by which time all infants were in sinus rhythm with age-appropriate heart rates and arterial pressure. Although we did not have any clinical problems, a loss of atrioventricular conduction in infants may have clinical significance because of the contribution of atrial contraction to stroke volume. This would be particularly important if airway problems and hypoxaemia developed during an inhalation induction, or if the infant were hypovolaemic.

In summary, the use of incremental or high-concentration sevoflurane for anaesthetic induction in unpremedicated infants was associated with a 20% incidence of nodal rhythm. This unexpected finding highlights the importance of using continuous ECG analysis when studying the side effects of volatile agents in young children.

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Estimation of pulmonary blood flow from sinusoidal gas exchange during anaesthesia: a theoretical study

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We simulated the use of simultaneous sinusoidal changes of inspired O_2 and N_2O (Williams *et al.*, *J Appl Physiol*, 1994; **76**: 2130–9) at fractional concentrations up to 0.3 and 0.7, respectively, to estimate FRC and pulmonary blood flow (PBF) during anaesthesia, using O_2 as an insoluble indicator. Hahn's approximate equations, which neglect the effect of pulmonary uptake and excretion on expiratory flow, estimate dead space and alveolar volume (V_A) with systematic errors less than 10%, but yield systematic errors in PBF which are approximately proportional to $F_{I_{N_2O}}$ in magnitude. A correction factor $(1-\bar{P})^{-1}$ for Hahn's equations for PBF (where $\bar{P}$ is the mean partial pressure of the soluble indicator) reduces the dependence of PBF estimates on $F_{I_{N_2O}}$, and the solution of equations describing the simultaneous mass balance of both indicators yields accurate results for a wide range of mean $F_{I_{N_2O}}$. However, PBF estimates are sensitive to measurement errors and a third gas must be present to ensure that the indicator gases behave independently.

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The sinusoidal frequency response technique for estimating pulmonary blood flow (PBF) was described by Zwart *et al.*[1] in 1976. The method has recently been extended by Williams *et al.*[2] in 1994 to allow simultaneous estimation of dead space, alveolar volume and PBF using insoluble (argon) and soluble (nitrous oxide: N_2O) indicator gases modulated in anti-phase at low mean inspired fractions. An important advantage of this technique is that the sinusoidal perturbation of the soluble indicator gas fraction in mixed venous blood is attenuated and can be ignored if the modulation frequency is high enough. In their analysis, Zwart *et al.*[1] imply that the sinusoidal forcing technique depends only on the modulation and is independent of the mean inspired fraction of the soluble indicator gas. Barton *et al.*[3 4] recognized the problem associated with large mean fractions of N_2O and suggested that the mean inspired fraction should be kept below 0.1 but did not assess the magnitude of the errors that result if the mean indicator fraction goes above 0.1.

Oxygen (O_2) has a very low blood–gas partition coefficient of 0.024 in fully saturated arterial blood. In healthy well oxygenated lungs, variations in alveolar P_{O_2} result in very small variations in pulmonary venous O_2 content when high haemoglobin saturation (P_{O_2}>100 mm Hg) is maintained. If $F_{I_{O_2}}$ is varied, then the O_2 flux from the airway into the alveolar compartment can be considered to consist of two components: a constant unidirectional flux which brings mixed venous blood to arterial saturation and a varying bi-directional flux which changes the fraction of O_2 in the alveolar compartment. Hahn[5] showed that if arterial haemoglobin is well saturated and oxygen uptake is constant, the constant unidirectional flux may be ignored and O_2 can be used as an approximately insoluble indicator gas for the measurement of lung volumes. This technique has been verified experimentally in healthy adults.[6]

It would be convenient if N_2O and O_2 could be used as indicator gases in the same concentrations as they are commonly used during anaesthesia. We analysed the sinusoidal technique theoretically and used detailed computer modelling of dynamic multi-component gas exchange to investigate the systematic errors in estimates of dead space, alveolar volume and PBF that result when the sinusoidal technique is used as published with mean inspired fractions of indicator gases (O_2 and N_2O) greater than 10% as is commonly the case during general anaesthesia.

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Patients and methods

Theoretical analysis

Equation (A1) (see Appendix) gives the mass balance of a soluble indicator gas in a perfectly mixed, single-compartment lung subjected to continuous ventilation and perfusion (Fig. 1). If both the mean concentration and the sinusoidal amplitude of the indicator gas are small, then equation (A1) can be simplified to yield a linear first-order differential equation (equation (A4)), as previously shown.[2] Neglecting the effects of the mean indicator concentration is equivalent to assuming that inspiratory and expiratory flows are identical,[3] and causes PBF to be underestimated by the factor $(1 - \bar{P})$ where $\bar{P}$ is the mean fraction of the soluble gas. The complete mass balance equation also contains a non-linear term which can be neglected when the modulation amplitude is small. A steady-state sinusoidal solution to the complete mass balance equation is derived (equation (A10)) to estimate PBF when the fraction of the soluble indicator gas is high and alveolar volume is known exactly. Alveolar volume can be estimated simultaneously from measurements of the partial pressure of an insoluble indicator gas modulated in anti-phase to the soluble indicator using equation (A8). However, it is preferable to consider the mass balances of the two indicator gases simultaneously. Equation (A13) is a frequency domain steady-state sinusoidal solution to the simultaneous mass balance equations (A11) and (A12), which can be solved simultaneously with equation (A10) to yield estimates of both alveolar volume and PBF.

If a lung is ventilated with a binary mixture of a soluble and insoluble indicator gas, then the sum of the partial pressures of the two gases always equals barometric pressure, if the small effects of carbon dioxide (CO_2) and water vapour are ignored. Any excursion of the partial pressure of one component is matched by an equal and opposite excursion of the partial pressure of the other component. Hence, in the alveolar gas, the magnitude of the peak sinusoidal excursion of the partial pressure of the insoluble gas is equal to that of the partial pressure of the soluble gas, regardless of their mean concentrations. Only one independent measurement can be made from a sinusoidally oscillating binary gas mixture and it is not possible to estimate two unknown parameters. Therefore, a binary mixture of soluble and insoluble indicator gases (e.g. the commonly used mixture of O_2 and N_2O) cannot be used to monitor alveolar volume and PBF simultaneously.

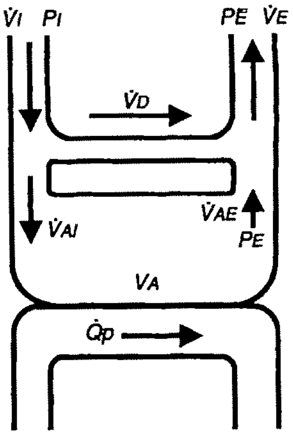

Fig 1 Diagrammatic representation of the computer model of the respiratory system V_I, V_E: total inspiratory and expiratory flows, respectively, $\dot{V}_{AI}$, $\dot{V}_{AE}$: alveolar inspiratory and expiratory flows, respectively; P_I, P_E, $P_{\bar{E}}$: partial pressure of indicator in inspiratory, alveolar and mixed expired gases, respectively; Q_p: PBF.

Computer simulation

Computer simulation was used to investigate the systematic errors introduced by the following assumptions in the derivation of Hahn's equations: (i) the indicator gases are present at low concentrations; (ii) the absorption of the soluble indicator gas does not affect expiratory flow; (iii) each indicator gas behaves independently of all the other gases in the lung. The computer model (see Appendix) comprises four simultaneous differential equations describing the mass balance of four gases (O_2, CO_2, N_2 and N_2O) in a single perfectly mixed constant-volume alveolar compartment subjected to continuous inspiratory ventilation $\dot{V}_I$ with a mixture of O_2, N_2 and N_2O. These equations describe the complete mass balance of the four gases and do not rely on the above assumptions. N_2O is exchanged with a constant PBF ($\dot{Q}_p$) and the mixed venous partial pressure of N_2O is kept constant at the mean inspired value. Hence, once steady-state sinusoidal equilibrium is reached by the model, the mean N_2O flux becomes zero. The body compartment is assumed to be large enough to filter out all perturbations in gas concentrations.[7] A proportion (30%) of the total inspiratory gas flow bypasses the alveolar compartment and mixes continuously with expired gas to represent dead space ventilation, leaving a net inspiratory alveolar flow of $\dot{V}_{AI}$. Shunted blood flow, lung tissue absorption of N_2O and the effects of water vapour are not included in the model as they do not influence the validity of this study. Constant oxygen consumption is modelled by the removal of oxygen from the alveolar compartment at a rate of 250 ml min^{-1}. CO_2 is added to the alveolar compartment at a rate equal to the O_2 consumption (RQ=1). Both N_2 (blood–gas partition coefficient=0.012) and O_2 (blood–gas partition coefficient in saturated blood=0.024) are assumed to be insoluble, and the blood–gas partition coefficient of N_2O is assumed to be 0.47. The sum of gas partial pressures is equal to atmospheric pressure at all times.

The model was implemented using Matlab and Simulink software (The MathWorks, Natick, MA, USA) and solved with the integration routine 'ode15' with variable step size and an absolute tolerance parameter of 1×10^{-6}.

The inspired gas composition was modulated sinusoidally with a peak-to-peak amplitude of 0.02 and a period of 120 s which has been suggested to be the optimum period for this technique.[8] Alveolar volume was maintained constant at 2.5 litres by adjusting the alveolar expiratory flow $\dot{V}_{AE}$ at each time step. The initial values of the gas fractions in the lungs were set to the mean inspired values and the model run for 1200 s to achieve steady-state sinusoidal conditions. The relative amplitudes and phases of the sinusoidal components of the inspired, mixed expired and end-expired indicator gas fractions were estimated from the last 120 s of the simulation by fitting the expression $P\sin(\omega t + \Phi)$ to simulated partial pressure values using the Gauss–Newton method (Matlab, The MathWorks), and these values were used to recover dead space using equation (A9). Alveolar volume and PBF were estimated from the amplitudes of the sinusoids using the following sets of equations (see Appendix): (i) equations (A9), (A8) and (A6) evaluated sequentially; (ii) equations (A9), (A8) and (A10) evaluated sequentially; and (iii) evaluation of equation (A9) followed by simultaneous solution of equations (A10) and (A13) by an interval bisection technique (Matlab, The MathWorks).

The simulation study was conducted in two parts using inspired gas mixtures comprising N_2O, O_2 and N_2 under the following conditions.

(i) N_2O was oscillated in anti-phase with N_2 such that $FI_{N_2O} + FI_{N_2}$ was constant. FI_{O_2} was not modulated. The mean FI_{N_2} was kept constant at 0.01 while the mean FI_{N_2O} was first set to 0.01 and then varied from 0.1 to 0.7 in steps of 0.1. FI_{O_2} was selected to make up the balance. This condition represents the case in which an inert gas (in this case N_2) is used as an insoluble indicator gas at low concentration, and N_2O as a soluble indicator gas at concentrations ranging between those typical of an indicator gas and those typical of an anaesthetic agent. These conditions were used to evaluate the performance of equations (A9), (A8), (A6) and (A10) as a function of mean FI_{N_2O} when the mean inspired fraction of the insoluble gas was low.

(ii) N_2O was oscillated in anti-phase with O_2 such that $FI_{N_2O} + FI_{O_2}$ was constant. The mean FI_{O_2} took values of 0.2, 0.25 and 0.3, while mean FI_{N_2O} was first set to 0.01 and then varied from 0.1 to 0.7 in steps of 0.1. FI_{N_2} was selected to make up the balance and was not modulated. This condition represents the case in which O_2 is used as an insoluble indicator gas at physiological concentrations and N_2O as a soluble indicator gas at concentrations ranging between that of a typical indicator gas and that of an anaesthetic agent. The per unit sensitivities of PBF to errors in alveolar volume and gas partial pressure measurements, and of alveolar volume to errors in partial pressure measurements were calculated numerically using a forward difference numerical technique as follows. If $y_0 = y(x_0)$ and $y_1 = y(x_0 + \Delta x)$ where Δx is small compared with x_0, then the per unit sensitivity of y to errors in x is given by

$$\frac{(y_1 - y_0)/y_1}{\Delta x/x_0}.$$

Each condition was simulated with PBF at values of 1, 5 and 10 litre min^{-1} and the recovered PBF compared with the true value. Only systematic errors (referred to in this report simply as 'errors') related to approximations in the simplified equations were assessed.

Results

The amplitudes and phases of the inspiratory, alveolar and mixed expiratory sinusoids were recovered with standard error of regression less than 2.5×10^{-6} atmospheres in all cases. The results obtained in the two parts of this study are as follows.

(i) When N_2 at a mean inspired fraction of 0.01 was used as the insoluble indicator gas, the absolute values of the systematic errors in estimates of dead space (equation (A9)) and alveolar volume (equation (A8)) were less than 0.5% for $0.01 < \text{mean } FI_{N_2O} < 0.70$. PBF calculated from simulation results by the approximate equation (equation (A6)) and plotted in Fig. 2 exhibited systematic errors which were negative and increased in magnitude in approximate proportion to increasing mean FI_{N_2O}. The systematic errors in the corrected equation (equation (A10)) were substantially smaller (less than 3.5%).

(ii) When N_2O was oscillated in anti-phase with O_2, at mean FI_{O_2} of 0.2–0.3, systematic errors in dead space were less than 2% in all cases. However, systematic errors in alveolar volume (equation (A8)), shown in Fig. 3, increased strongly with increasing FI_{O_2} and with

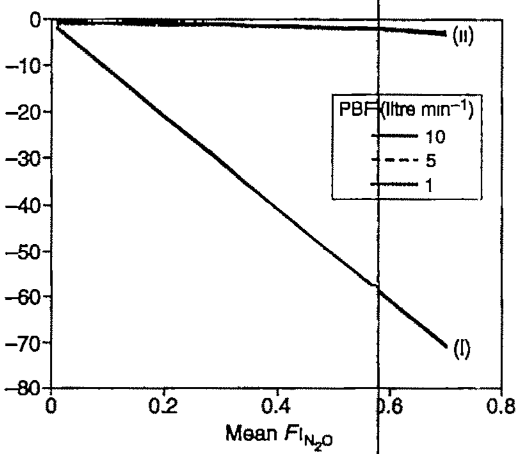

Fig 2 Systematic errors in PBF estimates when a low-concentration insoluble tracer gas (N_2) is used to monitor alveolar volume, and various mean concentrations of N_2O with O_2 as balance are used to monitor $\dot{Q}_p$ (i) Equations (A9), (A8) and (A6) evaluated sequentially (ii) Equations (A9), (A8) and (A10) evaluated sequentially. PBF, pulmonary blood flow.

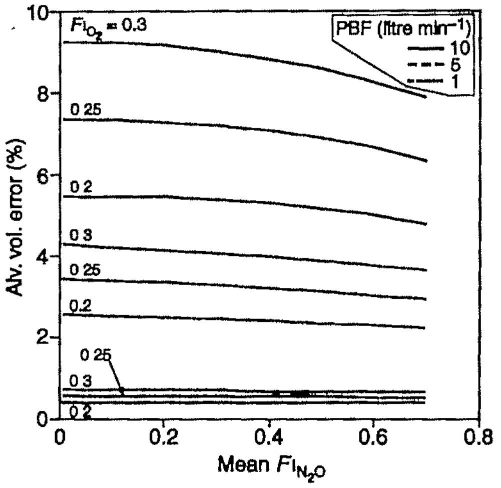

Fig 3 Systematic errors in estimated values of alveolar volume when the mean $F\text{I}_{O_2}$ was 0.20, 0.25 and 0.30, and PBF was 1, 5 and 10 l min^{-1}. Equations (A9) and (A7) were evaluated sequentially to estimate V_A.

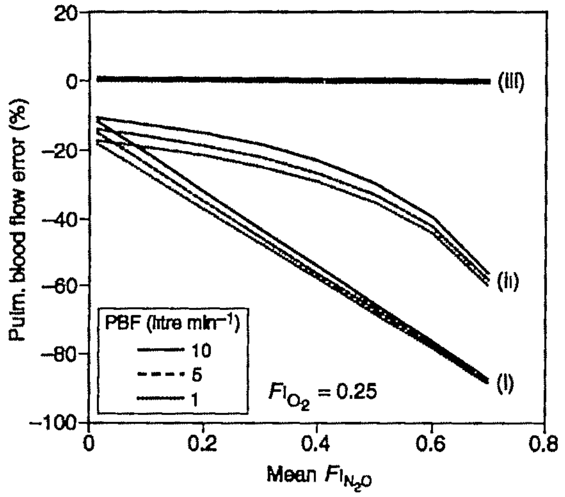

Fig 4 Systematic errors in PBF estimates when O_2 (mean $F\text{I}_{O_2}$ 0.25) is used as the insoluble tracer gas and N_2O as the soluble gas with N_2 as balance using: (i) equations (A9), (A8) and (A6) evaluated sequentially; (ii) equations (A9), (A8) and (A10) evaluated sequentially; and (iii) evaluation of equation (A9) followed by simultaneous solution of equations (A10) and (A13) by interval bisection

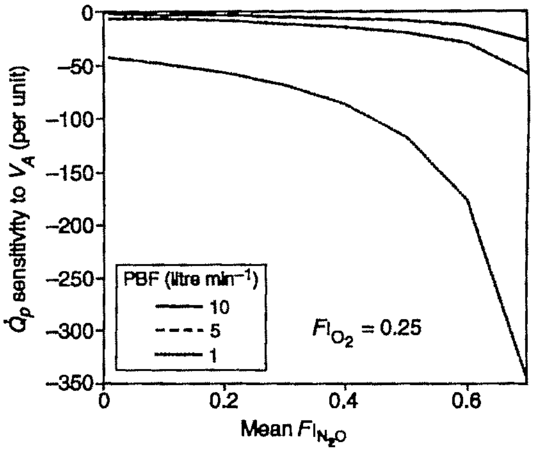

Fig 5 Per unit sensitivity of estimated PBF (using simultaneous equation (A10) to errors in alveolar volume calculated using a forward difference technique for $F\text{I}_{O_2}$ = 0.25 and balance N_2).

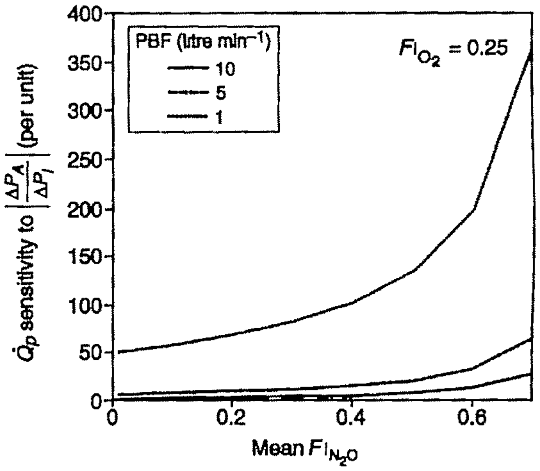

Fig 6 Per unit sensitivity of estimated PBF (using simultaneous equations (A10) and (A13)) to errors in the ratios of the magnitudes of the partial pressure of the indicator gases calculated using a forward difference technique for $F\text{I}_{O_2}$ = 0.25 and balance N_2 The sensitivities to O_2 and N_2O are almost identical, therefore only one curve is plotted at each PBF.

increasing PBF. PBF error depended weakly on the mean $F\text{I}_{O_2}$ and for clarity is shown in Fig. 4 for a mean $F\text{I}_{O_2}$ of 0.25 only. Equation (A10) performed substantially better than the approximate equation (equation (A6)) at low $F\text{I}_{N_2O}$ values, but deteriorated at high $F\text{I}_{N_2O}$. Figure 5, in which the sensitivity of PBF to errors in alveolar volume is plotted, suggests that the errors in PBF in curves (ii) in Fig. 4 were related to errors in alveolar volume. Equations (A10) and (A13) solved simultaneously yielded estimates of alveolar volume and PBF (curves (iii) in Fig. 4) within 1% of the true values for all mean concentrations of indicators studied. However, the sensitivity of this technique to measurement error is large, particularly when the PBF is low (Fig. 6). The sensitivity to measurement error of alveolar volume estimates obtained by simultaneous solution of equations (A10) and (A13), shown in Fig. 7, is substantially smaller.

Discussion

We have shown that while approximate solutions to the steady-state sinusoidal mass balance of a soluble indicator gas yield acceptable estimates when the mean concentrations of the indicators are small, modified solutions allow a greater range of mean indicator concentrations to be used.

The difference between the performance of equations (A6) and (A10) in Fig. 2 can be explained as follows. When

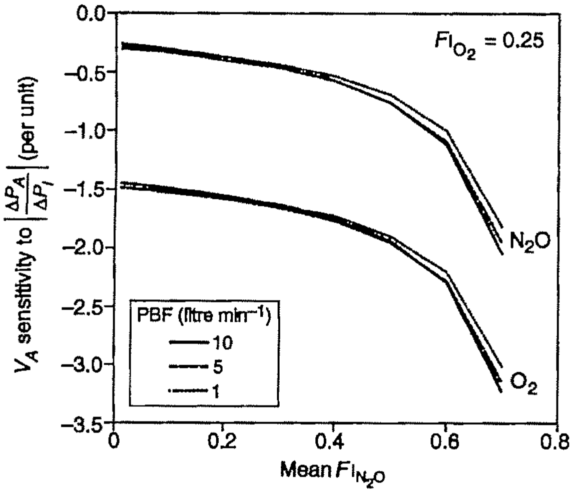

Fig 7 Per unit sensitivity of estimated alveolar volume (using simultaneous equations (A10) and (A13)) to errors in the ratios of the magnitudes of the partial pressures of the indicator gases calculated using a forward difference technique for $F\text{I}_{O_2}$ = 0.25 and balance N_2

the alveolar N_2O concentration exceeds its mean value, N_2O flows from the alveolar gas into the blood, causing expiratory flow to decrease. Similarly, a decrease in alveolar N_2O concentration causes expiratory flow to increase. Hence, there is a sinusoidal component of alveolar expiratory flow superimposed on the mean flow. In a subject in whom FRC is determined by the balance of elastic and muscular forces, we would expect to observe an equivalent behaviour superimposed on tidal gas movements. Expiratory flow carries N_2O out of the alveoli at a rate proportional to the absolute alveolar N_2O concentration, hence the sinusoidal component of the expiratory flow causes a sinusoidal flux of N_2O to be superimposed on the mean expiratory flux, disturbing the mass balance of N_2O in the lung in proportion to the mean N_2O fraction. In equation (A10) this effect appears as the modifying term $(1 - \bar{P})^{-1}$. When the inspired fraction of N_2O approaches 1 ($\bar{P}$ = 1), PBF causes no change in the alveolar partial pressure of N_2O and hence a 100% error results. The simplified mass balance equation (equation (A4)) is strictly true only when the indicator gas is present at negligibly low concentrations and modulated at very low amplitudes. Although the corrected equation apparently performs well under some conditions in the model study (curves (ii) in Fig. 2), the sensitivity to errors in measurements of the soluble gas concentration increases in inverse proportion to $(1 - \bar{P})$, hence this approach is impractical at high $\bar{P}$.

Equation (A13) is a complex (magnitude and phase) solution to the steady-state sinusoidal mass balance in the alveolar compartment when a soluble gas is modulated in anti-phase to an insoluble gas in the presence of at least one additional insoluble gas. If PBF is known, then equation (A13) can be solved for alveolar volume, or equations (A13) and (A10) can be solved simultaneously for alveolar volume and PBF when a third gas is present in the lungs.

When a non-respiring lung is ventilated with a modulated binary mixture of a soluble and insoluble indicator gas at constant barometric pressure, the modulation amplitudes of the indicators cannot be different. Hence, only one independent measurement can be made from which only one unknown can be estimated. In a respiring lung, the presence of CO_2 transforms the alveolar gas into a ternary mixture, and therefore in principle both volume and blood flow estimates are possible. However, the large sensitivity to measurement errors (Fig. 6) makes this approach impractical.

Figure 3 shows that when the insoluble indicator gas (in this case O_2) has a mean concentration greater than is typically used for indicator gases and is modulated at low amplitude in anti-phase with a soluble gas then substantial but perhaps clinically acceptable (less than 10%) systematic errors in lung volume estimates result, even when the soluble gas is at a low mean concentration These errors are approximately proportional to PBF and mean $F\text{I}_{O_2}$ and are caused by the sinusoidal component of the expiratory flow. These observations are related to the last term in equation (A12) which is neglected in equation (A8). When the interdependence between the indicator gases is not neglected (equation (A13)) the systematic errors are less than 1%, although the magnitude of the sensitivity to errors in O_2 measurements is greater than unity (Fig. 7). The sensitivity to errors in soluble gas measurements exceeds unity only when $F\text{I}_{N_2O}$ >0.5.

When the insoluble indicator gas is used at physiological inspired fractions (in this case O_2 at 0.20–0.30), the errors in PBF estimated by equation (A6) (Fig. 4) are similar in pattern but slightly larger in magnitude than those obtained with N_2 as insoluble indicator at an inspired fraction of 0.01 (Fig. 2). The negative bias of the corrected equation (A10) (curves (ii) in Fig. 4) results from errors in alveolar volume estimates (Fig. 3). Figure 5 shows that estimates obtained with equation (A10) are extremely sensitive to errors in alveolar volume under the conditions of this study, particularly at high $F\text{I}_{N_2O}$ and low cardiac output. When alveolar volume and PBF are estimated simultaneously from noise-free measurements of soluble and insoluble gases modulated in anti-phase, then the systematic errors in PBF are small. However, the sensitivity analysis (Fig. 6) suggests that this technique is extremely sensitive to measurement error, particularly at low values of PBF.

This study has identified an upper limit on the performance of the sinusoidal forcing technique under idealized conditions, but has not examined all possible causes of error. Effects that were ignored, including non-equilibrium of the soluble indicator gas throughout the body, the solubility of the indicators in lung tissue, pulmonary shunt and variations in O_2 consumption and in RQ, are likely to increase the uncertainty in estimates of cardiopulmonary variables. Pulmonary disease leading to maldistribution of ventilation and $\dot{V}/\dot{Q}$ mismatch, and variations in FRC during anaesthesia are also likely to cause additional systematic and random errors. Tidal breathing, the limited dynamic response of gas analysers and measurement noise limit the accuracy with which mixed expired and alveolar gas composition can be measured, and hence also adversely affect the uncertainty in the estimates, particularly when the alveolar plateau slopes steeply.

Conclusions

If soluble (N_2O) and insoluble indicator gases are used at low concentrations, and modulated at low amplitudes, then dead space, alveolar volume and PBF can be monitored simultaneously using simple closed-form equations and the magnitude of the per unit error in the PBF estimate is approximately equal to the inspired fraction of the soluble indicator. The $(1-\bar{P})^{-1}$ correction factor allows the closed-form equations to be used with mean alveolar N_2O fractions up to ~0.7 if the mean inspired fraction of the insoluble gas is low. If the mean inspired fraction of the insoluble gas is high (0.2–0.3), then estimates of PBF are biased low by ~20% when the mean inspired fraction of N_2O is low. In this case the dependence of estimates of PBF on mean FI_{N_2O} is reduced by the $(1-\bar{P})^{-1}$ correction factor for mean FI_{N_2O} less than ~0.3 and simple correction for the bias is possible. Simultaneous solutions to the mass balance of the two indicator gases allow alveolar volume and PBF to be estimated from noise-free measurements when the indicator gases are used at any mean concentrations in a ternary gas mixture, but the results are sensitive to measurement error, particularly at low PBF and high N_2O concentrations.

Acknowledgements

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Appendix

Glossary of symbols

Symbol	Description	Unit
s	Laplace variable	s^{-1}
t	Time	s
F	Fraction	—
$\bar{P}$	Mean partial pressure	Atmospheres
P(t)	Partial pressure (time variable)	Atmospheres
Q	Pulmonary blood flow	litres s^{-1}
V	Volume	litres
V	Volumetric gas flow	litres s^{-1}
Φ	Phase angle	radians
τ	Time constant of gas turnover in lungs	s
λ	Ostwald blood–gas partition coefficient	—
ω	Frequency	rad s^{-1}

Subscripts

atm	Atmospheric	E	Expiratory
m	Metabolic gas consumption or production	I	Inspiratory
p	Pulmonary	$\bar{V}$	Mixed venous
A	Alveolar	1	Soluble indicator gas
D	Dead space	2	Insoluble indicator gas

Equations for recovering lung volumes and pulmonary blood flow

With reference to the model in Fig. 1, the mass balance of a single indicator gas with blood–gas partition coefficient λ in a perfectly mixed single-compartment lung is given by:

$$V_A \frac{d}{dt} P_A(t) = \dot{V}_{AI} P_I(t) - \dot{V}_{AE}(t) P_A(t) + \lambda \dot{Q}_p [P_{\bar{V}}(t) - P_A(t)] \tag{A1}$$

where $P_I(t)$, $P_A(t)$ and $P_{\bar{V}}(t)$ are the time varying inspired, alveolar and mixed venous partial pressures of the indicator gas. Alveolar volume V_A and continuous inspiratory alveolar ventilation ($\dot{V}_{AI}$) are assumed to be constant. $\dot{V}_{AE}(t)$ is expiratory ventilation. Storage of indicator gas in lung tissue and pulmonary capillary blood is ignored.

In the absence of metabolic gas exchange, or if the respiratory quotient is unity, the alveolar expiratory flow can be written as:

$$\dot{V}_{AE}(t) = V_{AI} - \lambda Q_p (P_A(t) - P_{\bar{V}}(t)) \tag{A2}$$

where $\lambda \dot{Q}_p (P_A(t) - P_{\bar{V}}(t))$ is the volumetric rate of uptake of the soluble indicator gas (in this case N_2O) by the pulmonary blood.

Under steady-state sinusoidal conditions when the indicator gas is equilibrated throughout the instrumentation and all the tissues of the subject, then $P_I(t)$ and $P_A(t)$ can be written as $P_I(t) = \bar{P} + \Delta P_I(t)$, $P_A(t) = \bar{P} + \Delta P_A(t)$, respectively, where $\bar{P}$ is the mean partial pressure which is equal in all compartments, and $\Delta P(t)$ indicates the time-varying perturbation about the mean in each compartment. If the frequency of the sinusoid is high, the perturbations are strongly attenuated in the systemic circulation, and mixed venous content of the indicator gas is constant and $\Delta P_{\bar{\mathrm{V}}}(t) \approx 0$.

Substituting for $\dot{V}_{\mathrm{AI}}$, P_{I}, P_{A} and $P_{\bar{\mathrm{V}}}$ in equation (A1) and introducing the alveolar time constant $\tau = V_{\mathrm{A}}/\dot{V}_{\mathrm{AI}}$ yields:

$$\tau\frac{\mathrm{d}}{\mathrm{d}t}\Delta P_{\mathrm{A}}(t) = \Delta P_{\mathrm{I}}(t) - \Delta P_{\mathrm{A}}(t) - \frac{\dot{Q}_{\mathrm{P}}}{\dot{V}_{\mathrm{AI}}}\lambda\Delta P_{\mathrm{A}}(t)(1-\overline{P}) + \frac{\dot{Q}_{\mathrm{P}}}{\dot{V}_{\mathrm{AI}}}\lambda(\Delta P_{\mathrm{A}}(t))^2 \tag{A3}$$

If the perturbation amplitude is small and $\bar{P} << 1$, then equation (A3) reduces to:

$$\tau\frac{\mathrm{d}}{\mathrm{d}t}P_{\mathrm{A}}(t) = P_{\mathrm{I}}(t) - P_{\mathrm{A}}(t)\left(1 + \frac{\lambda\dot{Q}_{\mathrm{P}}}{\dot{V}_{\mathrm{A}}}\right) \tag{A4}$$

Equation (A4) is a linear first-order differential equation. Steady-state sinusoidal modulation of $P_{\mathrm{I}}(t)$ at a frequency ω rad s^{-1} results in sinusoidal perturbation of P_{A} with amplitude given by:

$$\frac{P_{\mathrm{A}}}{P_{\mathrm{I}}} = \left(\left(1 + \frac{\lambda\dot{Q}_{\mathrm{P}}}{\dot{V}_{\mathrm{A}}}\right)^2 + \omega^2\tau_{\mathrm{L}}^2\right)^{-\frac{1}{2}} \tag{A5}$$

Solving for $\dot{Q}_{\mathrm{P}}$ yields:

$$\dot{Q}_{\mathrm{P}} = \frac{\dot{V}_{\mathrm{A}}}{\lambda}\left(\left(\left|\frac{P_{\mathrm{I}}}{P_{\mathrm{A}}}\right|^2 - \omega^2\tau_{\mathrm{L}}^2\right)^{\frac{1}{2}} - 1\right) \tag{A6}$$

If the inspired indicator is insoluble ($\lambda = 0$) and the concentration of the soluble gas is negligible, then equation (A5) reduces to:

$$\frac{P_{\mathrm{A}}}{P_{\mathrm{I}}} = (1 + \omega^2\tau_{\mathrm{L}}^2)^{-\frac{1}{2}} \tag{A7}$$

Solving equation (A7) for alveolar volume yields:

$$V_{\mathrm{A}} = \frac{\dot{V}_{\mathrm{A}}}{\omega}\left(\left(\frac{P_{\mathrm{I}}}{P_{\mathrm{A}}}\right)^2 - 1\right)^{\frac{1}{2}} \tag{A8}$$

Alveolar ventilation $\dot{V}_{\mathrm{A}}$ is estimated by subtracting dead space ventilation $\dot{V}_{\mathrm{D}}$ from the total ventilation $\dot{V}_{\mathrm{E}}$. Dead space ventilation is given by:[2]

$$\frac{\dot{V}_{\mathrm{D}}}{\dot{V}_{\mathrm{E}}} = \frac{|P_{\bar{\mathrm{E}}}|\cos\Phi_{\bar{\mathrm{E}}} - |P_{\mathrm{A}}|\cos\Phi_{\mathrm{A}}}{P_{\mathrm{I}} - |P_{\mathrm{A}}|\cos\Phi_{\mathrm{A}}} \tag{A9}$$

where Φ_{A} and $\Phi_{\bar{\mathrm{E}}}$ are the phase differences between the inspiratory and alveolar, and inspiratory and mixed expiratory sinusoids, respectively, and $P_{\bar{\mathrm{E}}}$ is the amplitude of the sinusoidally modulated mixed expired partial pressure of the indicator gas. Equation (A9) is a form of the standard Bohr dead space equation.

Therefore, if the inspiratory concentration of an insoluble indicator gas is modulated sinusoidally about an arbitrary mean value and measurements of the amplitude and phase of the alveolar and mixed expiratory concentrations are made, dead space ventilation can be recovered using equation (A9) and alveolar ventilation estimated. Alveolar volume is estimated with equation (A8) and, if a soluble gas is oscillated simultaneously at low mean concentration, pulmonary blood flow can be estimated using equation (A6).

If $\bar{P}$ is not small then equation (A6) becomes:

$$\dot{Q}_{\mathrm{P}} = \frac{V_{\mathrm{A}}}{\lambda(1-\overline{P})}\left(\left(\left|\frac{P_{\mathrm{I}}}{P_{\mathrm{A}}}\right|^2 - \omega^2\tau_{\mathrm{L}}^2\right)^{\frac{1}{2}} - 1\right) \tag{A10}$$

Most of the Oxford work[2 6–8] subsequent to Barton's papers[3 4] is based on equations (A4)–(A9).

Simultaneous solution

Equation (A10) allows the estimation of pulmonary blood flow from measurements of inspired and alveolar partial pressures of a sinusoidally modulated soluble gas at any mean partial pressure less than one atmosphere, if τ is known. If we wish to estimate V_{A} simultaneously from measurements of an insoluble indicator gas modulated in anti-phase with the soluble gas, then the mass balances of the two gases must be considered simultaneously. Using the subscripts 1 and 2 to denote the soluble and insoluble gases, respectively, and neglecting second-order small terms, equation (A3) can be written as:

$$\tau\frac{\mathrm{d}}{\mathrm{d}t}\Delta P_{\mathrm{A1}}(t) = \left(\Delta P_{\mathrm{I1}}(t) - \Delta P_{\mathrm{A1}}(t)\right) - \frac{\dot{Q}_{\mathrm{p}}}{\dot{V}_{\mathrm{AI}}}\lambda\Delta P_{\mathrm{A1}}(t)(1-\overline{P}_1) \tag{A11}$$

for the soluble gas and

$$\tau\frac{\mathrm{d}}{\mathrm{d}t}\Delta P_{\mathrm{A2}}(t) = \left(\Delta P_{\mathrm{I2}}(t) - \Delta P_{\mathrm{A2}}(t)\right) + \frac{\dot{Q}_{\mathrm{p}}}{\dot{V}_{\mathrm{AI}}}\lambda\Delta P_{\mathrm{A1}}(t)\overline{P}_2 \tag{A12}$$

for the insoluble gas. Equations (A11) and (A12) must be satisfied simultaneously. Transforming to the Laplace domain under steady-state sinusoidal conditions and noting that $\Delta P_{\mathrm{I1}}(t) = -\Delta P_{\mathrm{I2}}(t)$ when the soluble and insoluble gases are modulated in anti-phase, equations (A10) and (Λ11) can be solved simultaneously to yield:

$$\frac{\Delta P^*_{\mathrm{A2}}(s)}{\Delta P^*_{\mathrm{I2}}(s)} = \left(\frac{\dot{V}_{\mathrm{AI}}}{sV_{\mathrm{A}} + \dot{V}_{\mathrm{AI}}}\right)\left(\frac{sV_{\mathrm{A}} + V_{\mathrm{AI}} + \lambda Q_{\mathrm{p}}(1-\overline{P}_1-\overline{P}_2)}{sV_{\mathrm{A}} + V_{\mathrm{AI}} + \lambda Q_{\mathrm{p}}(1-\overline{P}_1)}\right) \tag{A13}$$

where s is the Laplace variable and the superscript * indicates a transformed variable. Under steady-state sinusoidal conditions $s = i\omega$, where $i = \sqrt{-1}$. Equation (A13) allows V_A to be estimated from the magnitude of the ratio $\Delta P_{A2}/\Delta P_{I2}$ if $\dot{Q}_p$ is known. Both V_A and $\dot{Q}_p$ can be estimated if magnitude and phase components of equation (A13) are solved simultaneously. Alternatively, V_A and $\dot{Q}_p$ can be estimated by solving equation (A10) and the magnitude component of equation (A13) simultaneously.

The model

The model is based on four simultaneous equations describing the complete mass balance of O_2, CO_2, N_2O and N_2 in a constant-volume, single-compartment well mixed lung at constant temperature and pressure. No approximations are made other than to assume that all the gases obey the perfect gas law.

$$\frac{d}{dt}V_{A_{O_2}} = P_{I_{O_2}}(t)\dot{V}_{AI} - P_{A_{O_2}}(t)\dot{V}_{AE} - \dot{V}m_{O_2}$$

$$\frac{d}{dt}V_{A_{CO_2}} = P_{I_{CO_2}}(t)V_{AI} - P_{A_{CO_2}}(t)\dot{V}_{AE} - \dot{V}m_{CO_2}$$

$$\frac{d}{dt}V_{A_{N_2O}} = P_{I_{N_2O}}(t)\dot{V}_{AI} - P_{A_{N_2O}}(t)\dot{V}_{AE} + \lambda\dot{Q}_p\left(P\bar{v}_{N_2O} - P_{A_{N_2O}}(t)\right)$$

$$\frac{d}{dt}V_{A_{N_2}} = P_{I_{N_2}}(t)\dot{V}_{AI} - P_{A_{N_2}}(t)\dot{V}_{AE}$$

N_2 is assumed to be insoluble. $P\bar{v}_{N_2O}$ is assumed to be constant and equal to the mean inspired partial pressure of N_2. The total pressure in the alveolar compartment is always equal to atmospheric pressure:

$$P_{A_{O_2}}(t) + P_{A_{N_2}}(t) + P_{A_{N_2O}}(t) + P_{A_{CO_2}}(t) = P_{atm}$$

All gases are assumed to be ideal. For the *j*th gas:

$$P_{Aj}(t) = \frac{V_{Aj}(t)P_{atm}}{\sum_k V_{Ak}}$$

Inspiratory alveolar ventilation is given by:

$$\dot{V}_{AI} = (1 - F_D)V_I$$

Expiratory alveolar ventilation ($\dot{V}_{AE}$) is adjusted in each time step to maintain constant alveolar volume.

Total expiratory ventilation is given by:

$$\dot{V}_E(t) = \dot{V}_{AE}(t) + F_D\dot{V}_I$$

In the mixed expired gas the partial pressure of the *j*th component is given by:

$$P_{\bar{E}_j}(t) = \frac{P_{Aj}(t)\dot{V}_{AE}(t) + P_{Ij}(t)F_D V_I(t)}{\dot{V}_E(t)}$$

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Left ventricular pressure–area relations as assessed by transoesophageal echocardiographic automated border detection: comparison with conductance catheter technique in cardiac surgical patients

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The aim of this study was to validate measurements of intraoperative left ventricular (LV) area by transoesophageal echocardiography against simultaneous measurements of LV volume by conductance catheter (CC) in cardiac surgical patients with normal systolic LV function. Echo area was compared with CC volume during steady state and during acute changes of pre- and afterload by partial clamping of the inferior vena cava and the ascending aorta in eight patients scheduled for coronary artery bypass grafting. At steady state, Bland–Altman analysis of 32 recordings revealed a bias (SD) of 0.6% (2.5%) between echo area and CC volume, related to the initial values of end-diastolic area (100% area) and volume (100% volume), respectively. During loading interventions, bias between the two methods, as assessed by 112 measurement sequences, was 0.5% (3.7%) during aortic occlusion and –3.9% (4.4%) during cava occlusion at end-systole ($P<0.0001$); at end-diastole, this bias was 1.3% (4%) during aortic occlusion and 0.2% (5.7%) during cava occlusion ($P<0.0001$). Intraoperative area measurements with transoesophageal echocardiography in cardiac surgical patients with normal systolic LV function show good correlation with CC volume measurements under steady-state conditions. During acute unloading by vena cava occlusion, the resulting small end-systolic echo area measurements differ significantly more from CC volume measurements than during acute increase in afterload by aortic occlusion.

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Left ventricular (LV) pressure–volume loops are a useful measure of LV performance in a relatively load-independent manner.[1–4] In one animal[5] and two human[6 7] studies, loops acquired with an LV conductance and an LV pressure catheter were very similar under various conditions to those acquired with echocardiographic automated border detection and LV pressure. However, most of these authors used an echocardiographic border detection system manufactured by a single company; intraoperative validation of echocardiographic automated border detection with the conductance catheter (CC) method in humans has been reported by one group, so far.[6]

The aim of this study was to validate in humans intraoperative area measurements obtained by another type of automated echocardiographic system, using digital echo quantification (DEQ) against simultaneous volume measurements, obtained by an LV CC. Comparison of the two methods during cardiac surgery was undertaken to investigate the strengths and limitations of the intraoperative use of the DEQ method in patients with normal systolic LV function. We hypothesized that, during steady state and acute changes in loading, area changes measured with transoesophageal echocardiography at the mid-papillary short axis level would reflect accurately changes in CC volume.

Materials and methods

Patient characteristics

Following ethics committee approval and written informed consent, measurements were performed before and after

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cardiopulmonary bypass (CPB) in nine patients with stable coronary artery disease and normal LV ejection fraction undergoing coronary artery bypass grafting. None had akinetic or dyskinetic LV myocardial segments, two patients had discrete inferior hypokinesia and all subjects were in sinus rhythm. In one patient, echo quality in the short-axis view was not sufficient, so he was excluded from the study. The remaining eight patients (one female) had a mean age of 65 yr (95% confidence interval (CI) 61–69 yr) and an LV ejection fraction of 68% (95% CI 62–74%). Preoperative medication consisted of beta-blockers in seven patients, nitrates in four and calcium channel blockers in two; none of the patients was treated with ACE inhibitors.

Anaesthesia and operative techniques

Preoperative medication was continued until the morning of surgery. Patients were premedicated with oral flunitrazepam 0.02–0.03 mg kg^{-1}. In the operating room, a peripheral venous cannula and a fluid-filled femoral artery catheter (Seldicath, 1.3 mm; Plastimed, St-Leu-La-Forêt, France) were inserted under local anaesthesia. The arterial catheter was connected to a single-use transducer (Deltran II; Utah Medical Inc., Midvale, UT, USA). Continuous ECG (leads II and V5), arterial pressure and transcutaneous oxygen saturation monitoring were installed and connected to the monitoring system (Solar 8000; Marquette-Hellige GmbH, Freiburg, Germany). A continuous three-lead ECG was connected to the echo machine for DEQ signal-processing. Anaesthesia was induced with flunitrazepam (total dose 0.01–0.05 mg kg^{-1}) and fentanyl (total dose 25–55 μg kg^{-1}). Pancuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation, and patients' lungs were mechanically ventilated with a Servo 900C ventilator (Siemens Elema AB, Upplands Väsby, Sweden). Anaesthesia was maintained with propofol by continuous infusion (1.8–4.5 mg kg^{-1} h^{-1}). Central venous and pulmonary artery catheters (Baxter Intellicath 7.5 F; Baxter Healthcare Corp., Irvine, CA, USA) were placed via the right internal jugular vein, and the transoesophageal echo probe (see below) was inserted.

After sternotomy and pericardiotomy, epicardial pacemaker wires were fixed on the right atrium. After systemic heparinization, the aorta was cannulated, the CC was inserted via the right upper pulmonary vein and measurements were performed before right atrial cannulation.

Drug therapy for weaning from CPB consisted of nitroglycerine 0.6 (95% CI 0.26–0.94) μg kg^{-1} min^{-1} (six patients) or nifedipine 0.046 and 0.064 μg kg^{-1} min^{-1} (in two cases). In one case, norepinephrine 0.037 μg kg^{-1} min^{-1} was given for low systemic vascular resistance; no other catecholamine therapy was necessary in the study group. Propofol 3.3 (95% CI 2.6–4.1) mg kg^{-1} h^{-1} was used to maintain hypnosis during rewarming, chest closure and transfer to the intensive care unit.

Echocardiographic DEQ

Transoesophageal echocardiography with DEQ was done with an Omniplane 5 MHz echo probe and a Vingmed CFM 800 system (Vingmed Sound, Horten, Norway). We reduced overall gain, adjusted time gain, lateral gain compensations and compress levels and narrowed the image sector for optimal DEQ conditions and the highest possible frame rate (30–50 frames s^{-1}).[14] The DEQ uses high-quality two-dimensional (2D) images in a transgastric mid-papillary view; raw backscatter data are stored in memory and are subjected to a dynamic processing algorithm that applies statistically based edge-detection enhancement. A contour identifying the interface between blood and myocardium is superimposed on the real-time echocardiographic image and used for automated area calculation; it is displayed as a real-time trace in a manually tracked region of interest. The trace is exported as an analogue signal to an analogue–digital (A/D) converter and recorded with a sample rate of 1000 Hz on a workstation.

Conductance catheter

A 7 French, 12 electrode LV CC (Cordis Europa NV, LJ Roden, The Netherlands) with an integrated tip manometer (Sentron BV, AC Roden, The Netherlands) was introduced via the right upper pulmonary vein through the mitral valve with the help of an LV vent introducer and fixed with a purse-string suture. The catheter was advanced until four correct volume tracings were displayed on the screen of the CC monitoring system; its position within the left ventricle was controlled for centred radial position by transoesophageal echocardiography in a longitudinal view of the left ventricle. Tip manometer catheters were immersed in saline, then calibrated relative to atmospheric pressure; specific blood resistivity (ρ), which is defined as 1/blood conductance (σ), was measured before and after CPB with the help of a blood sample and the measuring cuvette supplied with the CC analysis system (Leycom Sigma 5 DF; CardioDynamics BV, Zoetermeer, The Netherlands). Injections of 12.5% saline into the distal port of the pulmonary artery catheter for determination of parallel conductance[2 3] were performed before and after CPB, immediately after determination of cardiac output with thermodilution (three to five injections of iced saline).

Data acquisition and registration

The ECG and femoral arterial pressure signals were amplified by the Solar 8000 monitoring system with a direct output to the A/D system. All analogue signals of interest (DEQ area, five CC volumes, micromanometer LV pressure, femoral arterial pressure and ECG were digitized with a sample rate of 1000 Hz for display and stored with the help of an A/D card and customized software under the environment of Superscope II (MacAdios; GW Instruments, Somerville, MA, USA) on an Apple Macintosh computer.

Compensation of the time used by the echocardiography system for calculation and display of DEQ was achieved by time-advancing the DEQ area curve until the first three to five beats of one 15 beat run were congruent to the CC volume signal. Compensation of the general, system-related, and the individual physiological time delay of a fluid-filled catheter against a rapid response micromanometer was performed by advancing the femoral arterial pressure curve until its ejection phases exactly matched the ejection phases of the LV pressure curve of the micromanometer.

To reduce electrical noise, all signals were filtered with a low-pass HAM filter with a 50 Hz frequency cut-off, signals >50 Hz being attenuated and those ≤50 Hz left unchanged.

Protocol

Simultaneous CC volume, DEQ area, LV and femoral arterial pressure signals were obtained during apnoea at end-expiration with zero positive airway pressure for 30 s. After a baseline measurement, one or two runs with injection of hypertonic saline into the distal port of the pulmonary artery catheter were then recorded. Acute alterations in preload were induced by partially clamping the inferior vena cava and afterload was increased by a partial aortic cross-clamping manoeuvre ('aortic occlusion'). Before CPB and after weaning from CPB and haemodynamic stabilization, we obtained duplicate measurements 5 min apart (i) during caval (Fig. 1A) and aortic occlusion (Fig. 1B) while the patient was in sinus rhythm, and (ii) with atrial pacing at a heart rate of 90 bpm. The registered LV pressure–volume and LV pressure–area loops were analysed off-line.

Data analysis

For steady-state analysis of DEQ area and CC volume, four runs per patient with optimal DEQ signal quality were chosen. Within these runs, three beats at the beginning or the end of the corresponding manoeuvre were analysed at 5 ms intervals, i.e. at a sampling rate of 200 Hz. For presentation of area data in cm^2, the stored analogue DEQ data were recalibrated using the end-diastolic and end-systolic values stored in the echocardiography system. Raw analogue output of the CC volume was calibrated for effective volume using the correction factor α with the help of the thermodilution-derived stroke volume as described previously.[4]

DEQ area and CC volume were normalized based on the first end-diastolic DEQ area (100% area) and CC volume (100% volume) values (Figures 3A and 4); values measured subsequently were expressed as a percentage of the initial end-diastolic values.

From individual runs during acute loading changes, 15 beats were selected: three to five beats before LV pressure changes and 10–12 during loading alteration.

For visual analysis, the DEQ signal (in mV) was calibrated for amplitude, baseline offset and time delay; the femoral arterial pressure curve was adjusted in time as described above. The LV pressure–area and LV pressure–volume loops were displayed for the selected beats. End-systolic and end-diastolic points of each loop were analysed. End-systole was measured at aortic valve closure, as determined by the femoral arterial pressure curve (Fig. 1), and at end-diastole at the end of the diastolic pressure plateau.

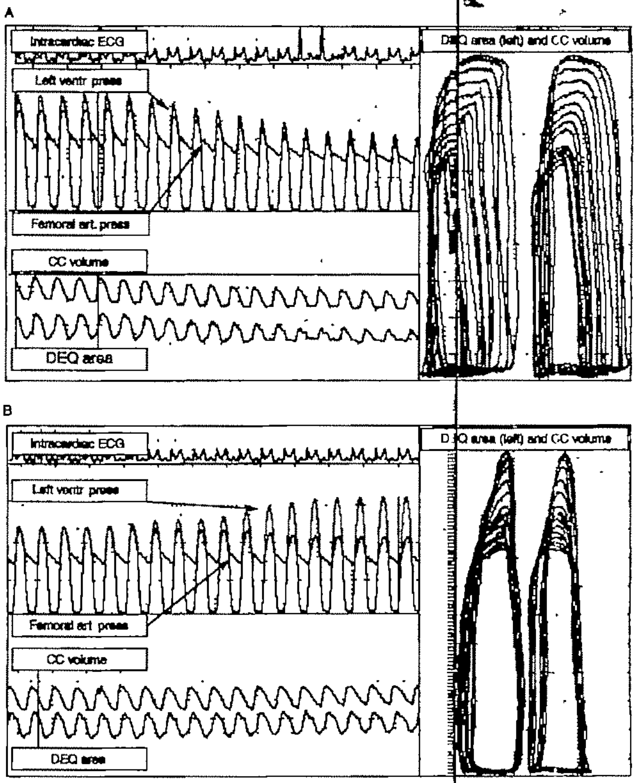


Fig 1 Manoeuvres for acute loading change partial clamping of (A) inferior vena cava and (B) ascending aorta. ECG=electrocardiogram, left ventr press=left ventricular pressure from the conductance catheter tip micromanometer, CC volume=conductance catheter volume, DEQ area=digital echo quantification

End-systolic and end-diastolic slopes of LV pressure plotted against DEQ area and CC volume, respectively, were calculated by linear regression analysis. All values of interest were exported to a data sheet for statistical analysis.

Statistics

Raw data are expressed as median and 95% CI; Bland–Altman analyses in the text are reported as mean (SD). Bland–Altman analyses and one linear regression analysis were used to present correlation of DEQ area and CC volume data. The significance of differences between measurements was determined using the Wilcoxon ranked sign test for paired comparisons and the Mann–Whitney *U*-test for unpaired comparison. *P* values <0.05 were considered significant. Calculations were made with Statview 4.5 (Abacus Concepts Inc, Berkeley, CA, USA).

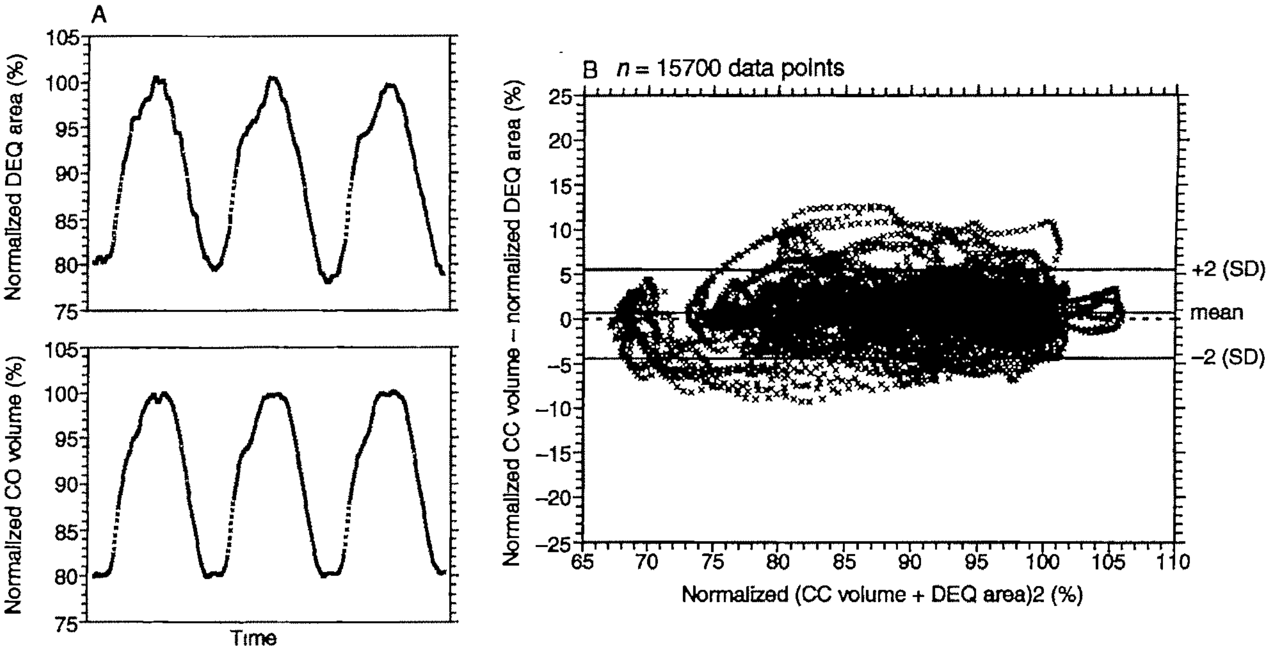


Fig 2 Simultaneous measurement of digital echo quantification (DEQ) area and conductance catheter (CC) volume at steady-state conditions Three consecutive beats per patient are shown Normalized DEQ area (%) and normalized CC volume (ml) are compared. Measurements were taken every 5 ms. (A) Example of a steady-state recording of normalized DEQ area (above) and normalized CC volume (below) during three cardiac cycles, adjusted for calculation time of DEQ area. (B) Bland–Altman analysis of normalized DEQ area and normalized CC volume. n=15 700 data pairs, 32 measurements (four per patient). For numerical values, see text

Results

General

A total of 174 measurements was performed. Forty-seven (27%) were not considered for analysis, 22 (12.6%) for technical reasons (improper partial clamping or declamping manoeuvre) and 25 (14.4%) because of insufficient transoesophageal echocardiograph image quality. Fifteen good-quality runs were randomly chosen not to be analysed for statistical reasons (not more than 16 runs per patient).

A total of 112 measurement runs of 15 beats each (median 14, 95% CI 12–14 runs per patient) was analysed during manoeuvres for acute loading changes (Fig. 1). For visual comparison with the CC volume data, amplification of the area signal was 9.5 (95% CI 8.4–10.6) times, baseline offset 7.2 (95% CI 4.8–9.6) mV and the area signal time offset compared with the CC volume signal was −194 (95% CI −202 to −168) ms.

Steady-state correlation of DES area and CC volume measurements

During steady state, curves of area changes as registered by DEQ showed a close agreement with curves obtained by the CC technique (Fig. 2): Figure 2A shows an example of parallel registration and Fig. 2B a Bland–Altman analysis of 32 steady-state recordings at 5 ms intervals; the mean (SD) difference between normalized DEQ area and normalized CC volume was 0.6 (2.5)%.

The difference between normalized end-systolic DEQ area and CC volume of these steady-state recordings was 1.0 (1.7)%; the end-diastolic difference was 0.3 (1.3)%.

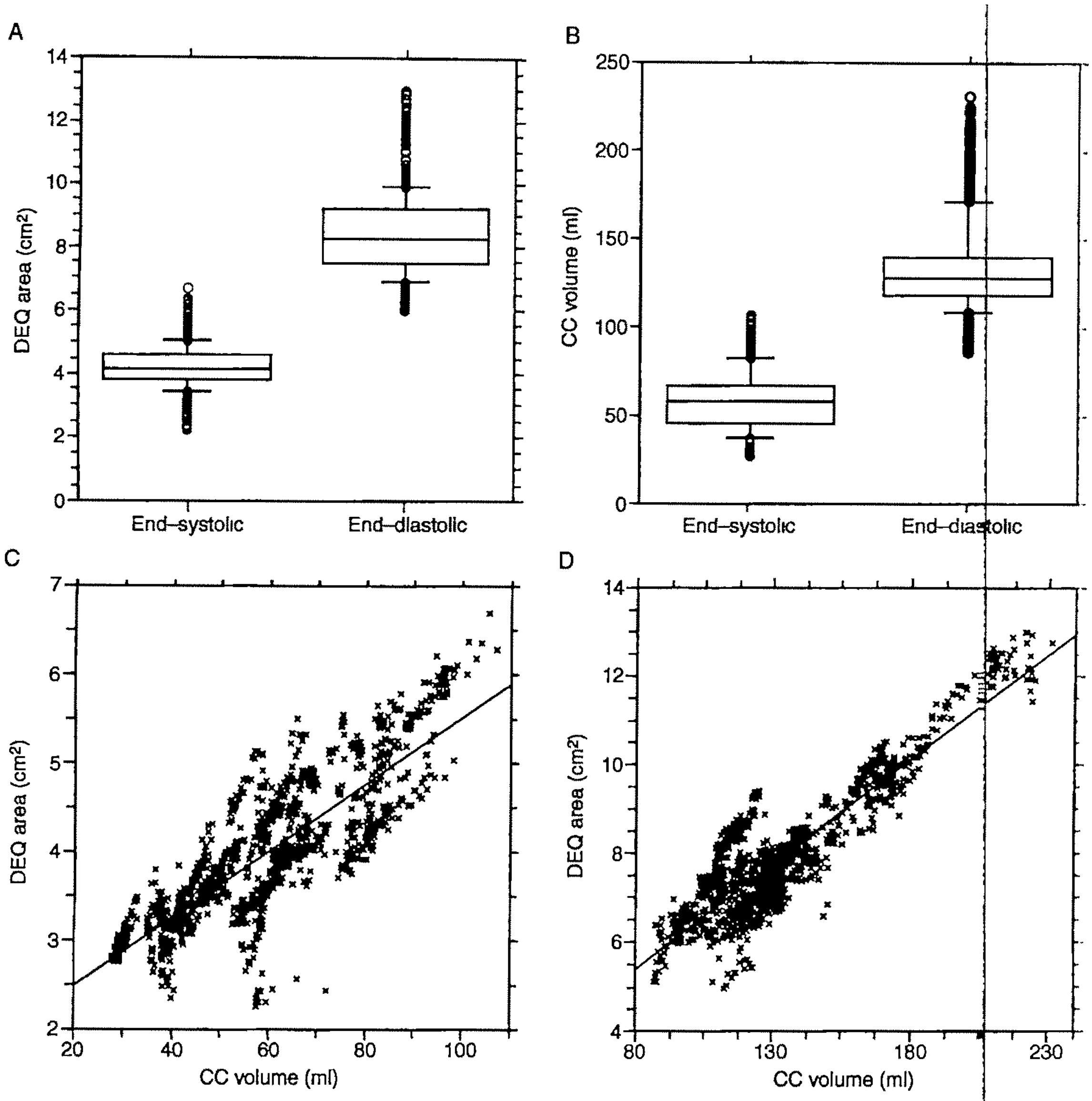
Correlation during interventions

DEQ area versus CC volume

Calibrated absolute DEQ area and CC volume values are presented as box plots (Fig. 3A,B) and as linear regression analyses (Fig. 3C,D). Numeric values are shown in Table 1.

DEQ area and CC volume during clamping are also expressed as normalized area and normalized volume, respectively. Bland–Altman analyses of the differences between normalized DEQ area and normalized CC volume of all 112 runs had an overall bias of −1.7 (5.1)% at end-systole and of 0.7 (5.0)% at end-diastole. The absolute difference was significantly greater at end-systole than at end-diastole ($P<0.0001$).

Figure 4 shows the same analysis for end-systole and end-diastole separately (panels A and B, respectively). Agreement was significantly less in the cava occlusion manoeuvre. The end-systolic difference was 0.5 (3.7)% and −3.9 (4.4)% during aortic and cava occlusion, respectively ($P<0.0001$ for absolute differences); end-diastolic difference was 1.3 (4)% and 0.2 (5.7)% during aortic and



DEQ area = 1.75 + 0.04 CC volume
$R = 0.83$, $P < 0.0001$

DEQ area = 1.65 + 0.05 CC volume
$R = 0.88$, $P < 0.0001$

Fig 3 Digital echo quantification (DEQ) area and conductance catheter (CC) volume measurements during interventions. (A and B) DEQ area in cm² (A) and CC volume in ml (B) at end of systole and end of diastole. Numerical values for the data plotted in (A) and (B) are given in Table 1 Box plots show isolated values and 10th, 25th, 50th, 75th and 90th percentiles. (C and D) Linear regression analysis of DEQ area versus CC volume at end of systole (C) and end of diastole (D) n=1680 data pairs.

cava occlusion, respectively (P<0.0001 for absolute differences).

Differences between pressure–area and pressure–volume slopes

Differences between slopes of elastance (end-systolic LV pressure in mm Hg)/(DEQ area in (cm²×10)) and (end-systolic LV pressure in mm Hg)/(CC volume in ml) during the two types of intervention are depicted in Fig. 5. These differences were significantly but not uniformly influenced by the type of clamping (aortic or cava occlusion). Elastance slope differences were significantly smaller during aortic occlusion (mean (SD) −0.2 (3.9) than during cava occlusion (−2.1 (8.4); P=0.03), whereas the slope differences for end-diastolic LV pressure plotted against DEQ area and CC volume, respectively, were higher during aortic occlusion (0.11 (0.85)) than during cava occlusion (0.26 (0.65); P=0.0013). The latter significance is only statistically important because the SDs of difference were very small with both manoeuvres.

Reproducibility of pressure–area versus pressure–volume slopes

For duplicate measurements, subsequent values are expressed as per cent changes from the first measurement to the second: elastance slope changes during aortic occlusion (LV

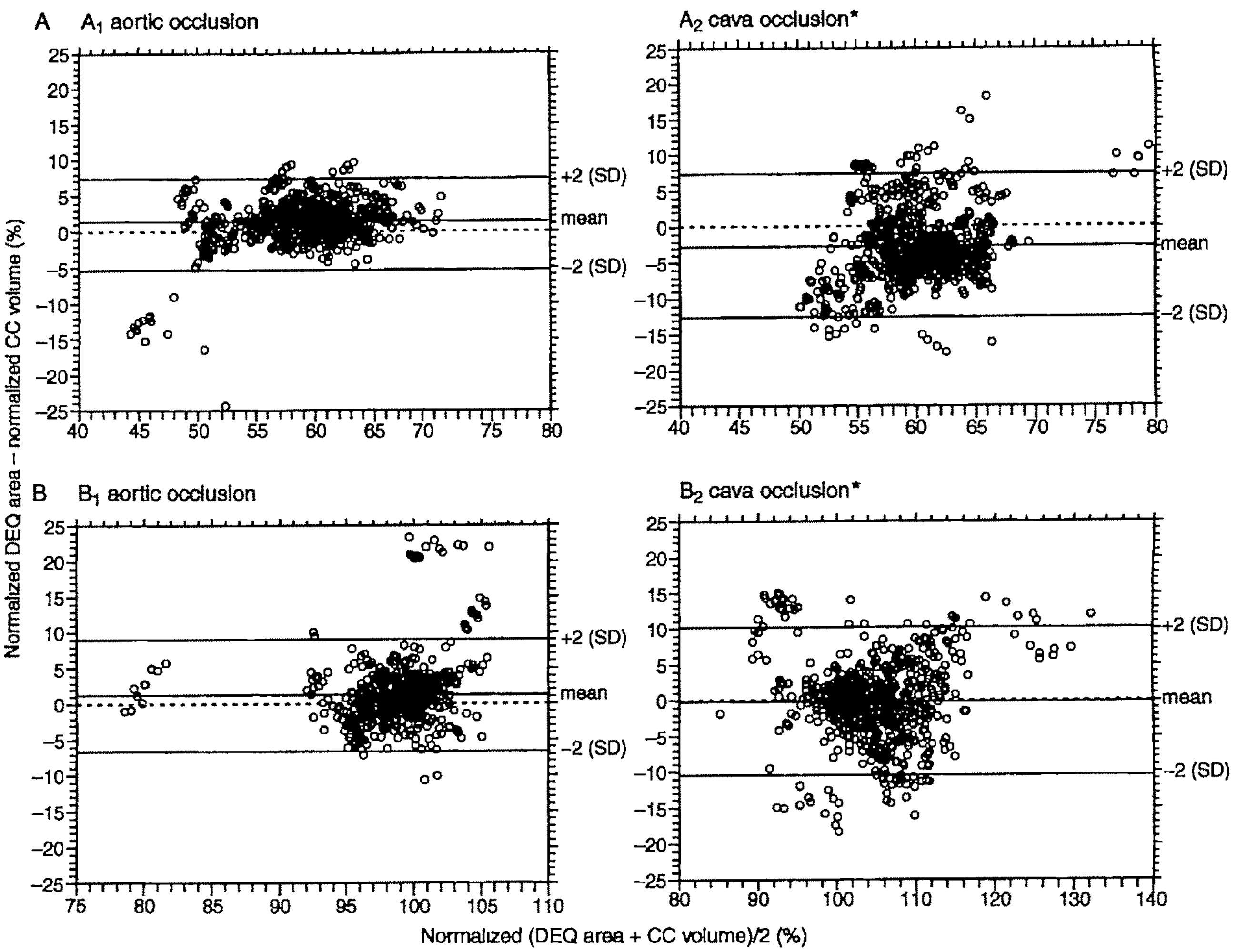


Fig 4 Bland–Altman analyses of normalized digital echo quantification (DEQ) area (%) versus normalized conductance catheter (CC) volume (%) during acute loading changes. There were 56 loading alterations with 15 data pairs each, giving 840 data pairs for aortic occlusion and 840 for cava occlusion. (A) End-systolic data pairs during aortic occlusion (A_1) and cava occlusion (A_2). (B) End-diastolic data pairs during aortic occlusion (B_1) and cava occlusion (B_2). *Absolute differences in aortic occlusion versus absolute differences in cava occlusion were significantly different ($P<0.0001$).

Table 1 Comparison of pre- and post-operative values. Data are presented as median (95% confidence interval) LV=left ventricular, DEQ=digital echo quantification; CC=conductance catheter, LVP=left ventricular pressure, FAC=fractional area shortening. *$P<0.05$ versus preoperative value. †$P<0.0001$ versus preoperative value

	Preoperative		Postoperative	
	End-systolic	End-diastolic	End-systolic	End-diastolic
LVP (mm Hg)	72 (71–73)	7.5 (7.3–7.7)	73 (72–74)	8.2 (8.0–8.4)*
DEQ area (cm^2)	3.5 (3.45–3.55)	7.2 (7.1–7.3)	4.1 (4.05–4.15)†	7.9 (7.7–8.2)†
CC volume (ml)	47.7 (46.6–48.8)	125.2 (124–126.8)	59.3 (58.1–60.5)†	131.2 (129.0–133.4)†
Slope				
LVP/DEQ area ((mm Hg)/(cm^2×10))	4.1 (2.4–5.8)	0.25 (0.09–0.41)	4.5 (3.3–5.7)	0.33 (0.11–0.55)
LVP/CC volume ((mm Hg) ml^{-1})	5.4 (3.5–7.1)	0.15 (0.01–0.29)	4.7 (3.9–5.5)	0.25 (0.18–0.32)
DEQ LV FAC (%)	51.0 (49.75–50.4)	50.0 (49.8–50.5)*		
CC LV ejection fraction (%)	60.1 (59.5–60.7)	55.3 (49.7–55.9)†		

pressure/DEQ area 32% (95% CI 9.5–54.5%) and LV pressure/CC volume 90.6% (95% CI 25–156.2%)) were significantly greater than during cava occlusion (LV pressure/DEQ area 14.4% (95% CI −7.0 to 36.1%) ($P=0.01$) and LV pressure/CC volume 31.1% (95% CI 10.0–51.2%) ($P=0.02$)). There was no significant difference between the two clamping manoeuvres for the end-diastolic pressure–area and pressure–volume slopes: for aortic occlusion, LV

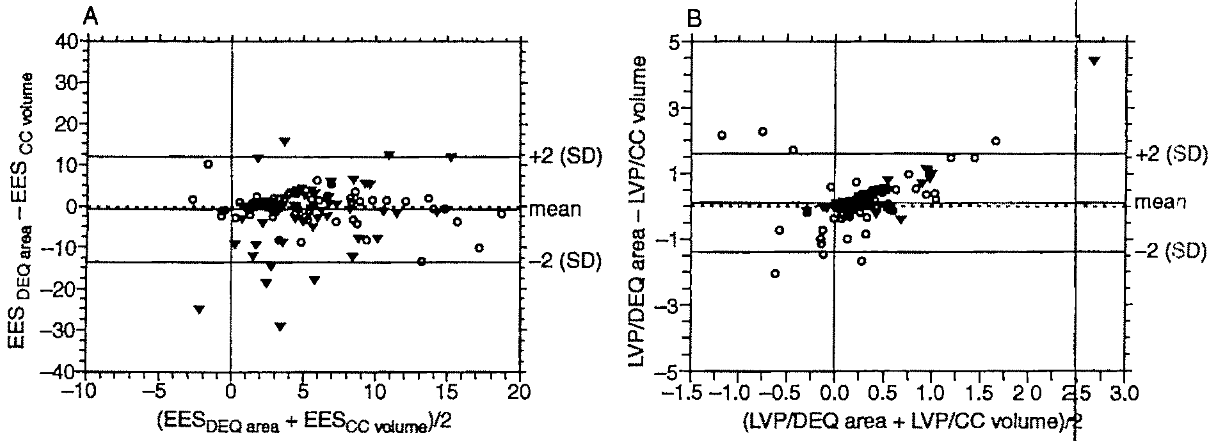


Fig 5 Bland–Altman analyses of slope differences Differences between micromanometer left ventricular pressure (LVP)/digital echo quantification (DEQ) area ((mm Hg)/(cm^2×10)) and micromanometer LVP/conductance catheter (CC) volume ((mm Hg)/ml). Fifteen data pairs were obtained for each of 56 loading alterations, giving 840 data pairs for aortic occlusion (open circles) and 840 for cava occlusion (filled triangles) For numerical values see the text. (A) End-systolic (elastance) slope (EES) differences (*P*=0.003 aortic occlusion versus cava occlusion) (B) End-diastolic slope differences (*P*=0 0013 aortic occlusion versus cava occlusion)

pressure/DEQ area was 13.6% (95% CI –89.9 to 117.1%) and LV pressure/CC volume was 31.3% (95% CI –1.7 to 64.3%); the corresponding values for cava occlusion were 8.2% (95% CI –13.4 to 29.8%) and 28.3% (95% CI 0.3–56.3%), respectively.

Effects of CPB and atrial pacing

Differences between preoperative and postoperative results are presented in Table 1. Pooled end-systolic and end-diastolic DEQ area and CC volume values were significantly larger after CPB than before CPB, and end-diastolic LV pressure was slightly, but significantly, higher.

The end-systolic LV pressure/DEQ area and LV pressure/CC volume slopes were the same before and after CPB; the end-diastolic LV pressure/CC volume slope increase following CPB was minimal, but statistically significant. DEQ LV fractional area change, CC LV ejection fraction and thermodilution measured stroke volume all decreased significantly after CPB.

The effects of atrial pacing are summarized in Table 2. Before CPB period, a heart rate of 90 beats min^{-1}, induced by atrial pacing, led to end-systolic and end-diastolic LV pressures being lower than those at spontaneous, lower frequency. All these differences were statistically significant, but very small. After CPB, only end-diastolic LV pressure decreased significantly when atria were stimulated at 90 beats min^{-1}.

DEQ-measured LV fractional area changes with or without atrial pacing were nearly identical before and after CPB; post-CPB values differed significantly from pre-CPB values, however. CC-volume based LV ejection fraction changes were larger during atrial pacing: a 4% increase was found before CPB while a 4% reduction resulted with pacing after CPB.

End-systolic pressure–area and pressure–volume slopes were not influenced by atrial pacing, either before or after CPB. End-diastolic pressure–volume slopes decreased slightly during atrial pacing before but not after CPB.

Early postoperative outcome

No early mortality, no new regional wall motion abnormalities (as assessed by intraoperative transoesophageal echocardiography) and no perioperative myocardial infarction (as assessed by ECG and cardiac enzymes) occurred. In one patient, transoesophageal echocardiographic examination led to a non-penetrating muco-serosal lesion of the oesophagogastric transition, as diagnosed by endoscopy in a previously unknown situs inversus abdominalis. The patient was discharged from the hospital on day 11 without sequelae. One patient developed postoperative pneumonia necessitating prolonged mechanical ventilation; his hospital stay was 18 days and his condition was good at discharge. Median postoperative stay in the intensive care unit was 1 0 day (95% CI 0.1–4.4 days); median hospital stay was 9.5 days (95% CI 7.2–11.8 days).

Discussion

Consistency of methodology and findings

The DEQ system gave reliable area measurements intraoperatively in cardiac surgical patients with normal systolic LV function. During steady-state conditions, the method accurately reflects volume changes measured with the CC method; during the two types of clamping manoeuvre, end-systolic and end-diastolic area measurements remain within ±10% of the CC volume method. The area measurements

Table 2 Effects of atrial pacing Data are presented as median (95% confidence interval) LV=left ventricular, ESP=end-systolic pressure; EDP=end-diastolic pressure, DEQ=digital echo quantification, FAC=fractional area shortening, CC=conductance catheter, EES=end-systolic elastance, ED=end-diasolic, LVP=left ventricular pressure $^{\dagger}P<0.05$ sinus rhythm versus atrial pacing, $^{\dagger\dagger}P<0.001$ sinus rhythm versus atrial pacing; $^{*}P<0.05$ preoperative versus postoperative atrial pacing; $^{**}P<0.0001$ preoperative versus postoperative atrial pacing; $^{\ddagger}P=0.0005$ preoperative versus postoperative sinus rhythm

	Preoperative		**Postoperative**	
	Sinus rhythm	**Atrial pacing**	**Sinus rhythm**	**Atrial pacing**
LV ESP (mm Hg)	76 (74–78)	69 (67–71)††	74 (72–76)	71 (69–73)*
LV EDP (mm Hg)	8.1 (8.0–8.2)	7.9 (7.8–8.0)††	9.1 (9.0–9.2)	7.3 (7.2–7.4)††
DEQ LV FAC (%)	50.6 (50.1–51.4)	49.1 (48.7–49.6)††	51.8 (51.4–52.2)	49.0 (48.6–49.2)†† *
CC LV ejection fraction (%)	56.8 (56–57.6)	60.9 (60.1–61.7)††	57.7 (56.7–58.7)	53.7 (52.9–54.5)†† **
EES				
LVP/DEQ area ((mm Hg)/(cm^2×10))	4.1 (2.0–6.1)	4.3 (1.4–7.2)	4.4 (2.6–6.2)	4.5 (2.9–6.1)
LVP/CC volume ((mm Hg) ml^{-1})	4.5 (2.2–6.8)	7.2 (4.6–9.8)	3.8 (2.8–4.9)	5.9 (4.7–7.1)
ED				
LVP/DEQ area ((mm Hg)/(cm^2×10))	0.3 (0.05–0.55)	0.18 (0.04–0.32)	0.43 (0.03–0.83)	0.27 (0.05–0.49)
LVP/CC volume ((mm Hg) ml^{-1})	0.19 (0.01–0.37)	0.11 (–0.1 to 0.32)†	0.27 (0.21–0.33)	0.24 (0.13–0.33)*
Heart rate (beats min^{-1})	71 (68.5–73.5)	90 (89–91)††	76 (73.2–78.8)	90 (88–92)†† ‡

obtained by the DEQ area method during cava occlusion are less precise than those obtained during aortic occlusion.

This is in accordance with the study of Chen and colleagues,[7] who used an identical echocardiography system but used a transthoracic approach for comparison with the conductance technique. In the apical four-chamber view, these authors based volume determination on automated digital echo quantification. We acquired the 2D images and, hence, the DEQ signal with a transoesophageal echo probe in a fixed position; patients were anaesthetized and measurements were taken at end-expiration. Stable images and good DEQ quality were, therefore, easier to obtain than with a hand-held transthoracic echo probe in spontaneously breathing patients. True cardiac volumes cannot be measured intraoperatively for validation of an echocardiographic volume or area determination. The CC measurements used in our study, however, have been shown to correlate with electromagnetic flow, thermodilution, contrast ventriculography, magnetic resonance imaging and ultrafast computed tomography in animals and in humans.[3,15,17] Although automatic border detection systems slightly underestimate fractional area changes by underestimating end-diastolic and overestimating end-systolic areas, compared with ultrafast computed tomography,[19] several studies have shown good correlation between the echocardiographic automated border detection and (i) real volume changes in an isolated canine heart preparation[18] and (ii) CC measurements in humans.[6,7]

Limitations of methodology and critical evaluation of results

Conductance catheter method

Theoretical and animal studies have shown that the accuracy of the CC method depends on the distance between the catheter and the wall of the ventricle, relative to the distance between the catheter injecting electrodes.[15,20–23] With larger ventricular volumes and, hence, in diastole, the method thus becomes less precise. We did not find this relevant in our study; on the contrary, differences between end-systolic volume and area measurements were significantly greater than differences at end-diastole.

Another source of error was found by Szwarc and colleagues.[27] Parallel conductance changes within cardiac cycles led to volume measurements being significantly different from those obtained by magnetic resonance imaging in an animal model. This was not considered to be of importance by Lankford and colleagues[24] or White and colleagues[25]

The metallic retractor in the open chest situation seems to be another source of artefacts for CC signals. Cabreriza and colleagues[26] found that isolation of the heart by latex wrapping could improve the reliability of volume signals. This isolation procedure, however, was introduced primarily to decrease the changes in parallel conductance, which is of importance only for absolute volume measurements. Another potential source of artefacts is the transoesophageal echo probe near the CC. We did not find that conductance signals were affected by whether the echo probe was emitting sound or not and this problem has not been reported by other investigators.

Echocardiography

During intraoperative monitoring, the mid-papillary short-axis view is widely accepted for the evaluation of LV filling state and contractility. Our aim was to validate intraoperative DEQ measurements in this standard plane against a well established method of LV volume determination. We found a small difference between the two methods within cardiac cycles. Following normalization of the DEQ area and correction for time delay, we found a cycle-specific pattern of under- and overestimation by DEQ (Fig. 3A), which supports the observations of Chen and colleagues.[7]

An important source of error in DEQ detection is the presence of the metal-containing CC in the ventricle. The echo probe had to be positioned carefully to avoid refraction and shadowing artefacts; the probe was then fixed using a specially designed apparatus. Nevertheless, DEQ area measurements were often blurred by the shadow of the CC, requiring exclusion of the catheter artefact area; particularly during the cava occlusion manoeuvre, lateral displacement of the hypovolaemic heart further impaired proper area detection. The measured LV area was therefore very small at the end of caval occlusion in a considerable number of patients, especially in those patients with small left ventricles at baseline. These artefacts probably led to spreading of the end-systolic area values during caval occlusion (Fig. 4) and the consequent spreading of elastance slope values.

Another difficulty of repeated 2D measurements is the reproducibility of the transgastric mid-papillary short-axis view. Although the probe was not moved during the measurement sequence, it cannot be guaranteed that its position was identical before and after CPB. However, each loading manoeuvre was analysed individually with regard to the area–volume relationship, and differences in area parameters before and after CPB are mirrored in CC volume measurements (Table 1).

Study patients had normal LV function without akinetic or dyskinetic wall segments and were therefore ideal for DEQ measurements. It is evident that the more regional wall motion abnormalities there are, the more bias there will be when any 2D measurements are compared with measurements of cardiac volumes.

Data analysis

Two methods were used to analyse differences between DEQ area and CC volume curves. During steady state, differences between filling and emptying patterns of LV were evaluated, the difference between each data pair being determined every 5 ms throughout the cardiac cycle. Although it would have been of interest to examine entire cardiac cycles during clamping manoeuvres too, this was not possible because of large quantities of data, so we restricted analysis of clamping manoeuvres to the clinically important time points of end-systole and end-diastole.

Calibration of the CC data for absolute volume was performed using the stroke volume derived from thermodilution measurements. This method is widely accepted; additional calibration with the saline dilution technique for parallel conductance did not seem to improve precision in our study. Variation of differences between normalized DEQ area and normalized CC volume data, however, was independent of calibration method.

We used a visually based, manually performed adjustment of the DEQ area curve. The time delay between registration of DEQ area and CC volume was variable and longer than reported with other automated border systems[5,9,11,25] (Fig. 1). Technically, the time delay depends on the time the system requires for calculating DEQ; physiologically, it depends on the position of the echo probe. The more apical data are acquired, the later the area curve is displayed, as compared with the CC volume curve. End-systole and end-diastole were determined manually based on the femoral arterial pressure curve (aortic valve closure) and on LV pressure. ECG was not taken into consideration as future analyses will be performed in patients with possible bundle-branch block or ventricular pacing.

Clamping manoeuvres

Partial occlusion for acute reduction in preload is widely accepted[4,5,7,9,10] and, although a partial aortic occlusion manoeuvre has been performed in animals[22] it is not to our knowledge a standard procedure in humans. By rapidly increasing LV afterload, it assesses the capacity of the left ventricle to maintain stroke volume against an increased aortic resistance without ventricular dilation. The so-called homeometric autoregulation capability[28,29] should leave end-diastolic volume and pressure unchanged.

Reproducibility

It is difficult to repeat partial clamping of the inferior vena cava and the ascending aorta for quantitative comparison. We controlled the clamping manoeuvres on line and the surgeon tried to get a similar decrease or increase in LV pressure. Nevertheless, the resulting pressure–area and pressure–volume slopes at end-systole yielded considerable variations, those of the pressure–area loops being significantly greater.

Findings

One patient presented insufficient correlation during the caval occlusion manoeuvre despite excellent DEQ quality. One of the reasons was insufficient clamping of the vena cava inferior, which led to a relatively small decrease in LV volume, correctly measured by CC, but not detected by the DEQ method in the 2D short-axis view. The consecutive DEQ elastance revealed an opposite slope to the corresponding CC elastance slope. During aortic occlusion, only very small volume changes but important LV pressure changes are induced. Slopes are therefore determined more by the increase in LV pressure than by (the virtually unchanged) LV area and volume; the correlation of the pressure–area with the pressure–volume is therefore superior than during the cava occlusion manoeuvre.

Conclusions

We found that intraoperative changes in LV volume, assessed by CC, are reliably reflected by transoesophageal echocardiographic DEQ area changes of the LV short axis during steady-state conditions and during acute increase of afterload by partial occlusion of the ascending aorta.

When very small systolic area values resulted from partial occlusion of the vena cava, the decreased precision of the

DEQ method made it difficult to perform reproducible end-systolic LV pressure–DEQ area elastance slopes.

Patients with enlarged left ventricles and reduced ejection fraction might present more favourable conditions for LV function evaluation with vena cava occlusion manoeuvres and DEQ area measurements.

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Effects of amrinone on ischaemia–reperfusion injury in cirrhotic patients undergoing hepatectomy: a comparative study with prostaglandin E_1

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The effects of amrinone, a selective phosphodiesterase III inhibitor, on liver ischaemia reperfusion injury have not yet been clarified. Forty-five patients with hepatocellular carcinoma who underwent partial liver resection using Pringle's manoeuvre were studied. Patients were divided into three groups: those given amrinone, those given prostaglandin E_1 (PGE_1) and those not treated (controls). An indocyanine green (ICG) clearance test was performed before the operation and three times during surgery: just before induction of liver ischaemia, just after liver resection and 60 min after reperfusion. Blood lactate and base excess were measured at the same times. Systolic and diastolic arterial pressure, heart rate, cardiac index and oesophageal temperature were monitored. Aminotransferase levels were recorded the day before surgery, 1 h after operation and on the first and third postoperative days. These data were compared between groups. The ICG elimination rate, lactate and base excess in the amrinone group differed significantly from those in controls during the observation period (P=0.03, P=0.04 and P=0.03, respectively). The differences between the PGE_1 and control groups were not significant. There were no significant differences between the groups in perioperative vital signs, cardiac index or postoperative aminotransferase. Amrinone enhanced intraoperative ICG elimination in cirrhotic patients who underwent liver resection.

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Amrinone is a non-catecholamine, non-glycoside drug with combined positive inotropic and vasodilating properties. Its mechanism of action is mediated by selective phosphodiesterase III enzyme inhibition, which increases cyclic adenosine 5′-monophosphate (cAMP) in both vascular smooth muscle and myocardium by preventing the degradation of cAMP. Increased cAMP increases muscle contraction by increasing myocardial intracellular calcium available from the sarcoplasmic reticulum. In contrast, in vascular smooth muscle cells, increased cAMP decreases intracellular calcium through an increase in calcium resequestration into the sarcoplasmic reticulum, producing relaxation and vasodilation. Since amrinone not only augments cardiac contractility but also reduces preload and afterload, it has been used to treat heart failure.[1]

In addition to its therapeutic effects in heart failure, amrinone appears to be ideal for treating peripheral circulatory disorders and improving viability of ischaemic tissues,[1] so we thought that it might also be useful for treating ischaemic liver. This study was designed to evaluate the effects of amrinone on the function of liver damaged by ischaemia–reperfusion injury. To evaluate liver function during hepatectomy involving liver ischaemia, indocyanine green (ICG) clearance and blood lactate concentrations were measured. ICG clearance[2 3] is an indicator of the metabolic function of the liver and of liver blood flow. The effects of amrinone on intraoperative liver function were compared with those of prostaglandin E_1 (PGE_1), which has been reported to improve liver dysfunction after ischaemia–reperfusion injury.[4]

Patients and methods

The study protocol was approved by the ethics committee of our local authority. Informed consent was obtained from each patient.

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Patients

From April 1998 to October 1999, 142 patients underwent hepatectomy at the Hepatobiliary Pancreatic Division, Department of Surgery, Tokyo University Hospital. Resectability was assessed and the surgical procedure was selected by following an algorithm based on three parameters: the presence or absence of ascites, total serum bilirubin concentration and ICG clearance.[5] Patients with no ascites, a serum total bilirubin concentration of <2.0 mg dl^{-1} (34 mmol $litre^{-1}$) and an ICG elimination rate (ICG-K) of >0.06 units min^{-1} were selected for surgery. ICG-K is a rate constant defined as the plasma ICG elimination rate.[6]

Forty-five patients (37 males and eight females, aged 48–76 yr) were included in this study. All patients were classified as ASA physical status II. To lessen the heterogeneity of the patient population and to exclude patients with severe cirrhosis, the inclusion criteria were defined as follows: (i) subjects were cirrhotic with hepatocellular carcinoma; (ii) tumours were limited to one segment according to Couinaud's nomenclature for liver segmentation;[7] (iii) either subsegmentectomy[8] or limited resection of the tumour was scheduled; (iv) Pringle's manoeuvre was used to induce liver ischaemia. In our institution, Pringle's manoeuvre is usually applied during hepatectomy to reduce blood loss. Briefly, the hepatoduodenal ligament was clamped using Fogarty forceps for 15 min to interrupt portal and hepatic arterial blood supply. This was followed by a 5 min release period. This schedule was repeated until liver resection was accomplished.[9]

Limited resection requires non-anatomical resection of the tumour(s) with an adequate margin of surrounding non-tumourous liver tissue. Subsegmentectomy requires complete anatomical resection of that subsegment of liver which is fed by the same portal branches. The method used by our surgical team to identify the subsegment in question has been described in detail elsewhere.[10] Patients were excluded if intraoperative ultrasound revealed tumour extension beyond one segment or if a procedure other than Pringle's manoeuvre was applied to induce ischaemia.

The patients who fulfilled these criteria were divided randomly into three groups. The randomization, which was done after the initial laparotomy and intraoperative ultrasound, was done by a permuted block design without stratification. The patients in the amrinone (n=15) and PGE_1 groups (n=15) received an intravenous infusion of amrinone (Amcoral; Meiji Pharmaceutical Co. Ltd, Tokyo, Japan) or PGE_1 (Prostandin; Ono Pharmaceutical Co. Ltd, Osaka, Japan), respectively, through a central venous catheter at a rate of 4.0 or 0.02 μg kg^{-1} min^{-1}, respectively. The amrinone or PGE_1 infusion was initiated at the start and terminated at the end of surgery. The 15 patients in the control group received neither drug. No placebo was administered to the control group as it was difficult to prepare one, because of the yellowish colouring agent contained in Amcoral.

Preoperative risk factors included hypertension in one patient in the amrinone group, one patient with diabetes mellitus and one with hypertension in the PGE_1 group, and one case each of hypertension and arrhythmia in the control group. Clinical and surgical details of the patients are given in Tables 1 and 2, respectively.

Anaesthesia

Anaesthesia was induced with midazolam 0.05–0.1 mg kg^{-1}, thiopental sodium 2–4 mg kg^{-1} and fentanyl 2 μg kg^{-1} and maintained with 0.8–1.5% end-tidal isoflurane, 50% nitrous

Table 1 Clinical details (number, range (median) or mean (SD))

	Control (n=15)	Amrinone (n=15)	PGE_1 (n=15)	P value
Gender (male:female)	12:3	12:3	13:2	0.99
Age (yr)	61–78 (68)	48–73 (65)	48–75 (65)	0.50
ICG-K (min^{-1})	0.12 (0.4)	0.13 (0.4)	0.12 (0.3)	0.97
AST (IU $litre^{-1}$)	56.9 (19.8)	48.0 (22.4)	57.1 (19.7)	0.61
ALT (IU $litre^{-1}$)	45.0 (26.8)	46.2 (21.5)	56.9 (20.1)	0.34
Albumin (g dl^{-1})	3.6 (0.4)	3.6 (0.3)	3.5 (0.4)	0.67
Prothrombin time (s)	11.9 (0.4)	11.7 (0.7)	11.8 (0.5)	0.19

Table 2 Surgical details (mean (SD))

	Control (n=15)	Amrinone (n=15)	PGE_1 (n=15)	P value
Duration of pre-ischaemic phase (min)	163 (77)	173 (114)	176 (76)	0.82
Duration of ischaemic phase (min)	70 (38)	66 (49)	71 (46)	0.89
Duration of surgery (min)	399 (118)	412 (144)	428 (152)	0.57
Blood loss (ml)	597 (543)	587 (470)	618 (413)	0.94
FFP transfusion (ml)	881 (402)	849 (532)	797 (441)	0.57
Fluid transfusion (ml)	1308 (471)	1256 (402)	1389 (382)	0.88
Weight of resected liver (g)	150 (200)	146 (167)	164 (174)	0.77

oxide in oxygen, and fentanyl 1–2 μg kg^{-1} h^{-1}. Muscle relaxation was maintained with pancuronium bromide 0.08 mg kg^{-1} h^{-1}. Mechanical ventilation was set at a respiratory frequency of 10–15 min^{-1} and an inspiratory/expiratory duration ratio of 1:2. The respiratory tidal volume was reduced to about 60% just before starting liver resection to reduce the thoracic and right atrial pressure and, consequently, back-bleeding from the hepatic veins and their tributaries.[5] The concentration of inspired oxygen was set to give an arterial oxygen tension of >120 mm Hg. The arterial carbon dioxide tension was maintained at 35–45 mm Hg. Invasive arterial pressure, heart rate and electrocardiogram (five leads and two channels: II and V5), pulse oximetry, end-tidal carbon dioxide tension and oesophageal temperature were monitored routinely.

Crystalloid infusion was kept to a minimum (4–4.5 ml kg^{-1} h^{-1}) to avoid sodium retention. Fresh frozen plasma was transfused when necessary to maintain stable haemodynamics. Packed red cells or fresh whole blood was transfused as required.

Data collection

One of the authors (M.H.) determined grouping and loaded an infusion pump with a blank, amrinone or PGE$_1$ syringe. Each syringe was covered with a black sheet so that it could not be seen by the surgeon or the anaesthetist. M.H. supervised the anaesthetist in charge of anaesthetic and exerted discretion in the event of complications resulting from the study drugs.

The following variables were recorded by the anaesthetist in charge of the anaesthetic. An ICG (Diagnogreen; Daiichi Pharmaceutical Co., Tokyo, Japan) test was performed before surgery, as a baseline (t_0), and three times during surgery, just before the induction of liver ischaemia by Pringle's manoeuvre (t_1), just after reperfusion of the liver, i.e. the completion of liver resection (t_2) and 60 min after reperfusion (t_3). Preoperative ICG-K was measured conventionally; ICG 0.5 mg kg^{-1} was injected intravenously, blood was sampled 5, 10 and 15 min after injection and the plasma concentration of ICG was measured using the method of Nielsen.[11] The blood concentration of ICG (in μg ml^{-1}) decreases exponentially with time (in minutes). The logarithm of the slope of the ICG versus time plot gives the elimination constant for ICG. During surgery, as it was not always possible for the anaesthetist in charge of the anaesthetic to take a blood sample exactly 5, 10 and 15 min after injection, pulse dye densitometry was used for ICG-K measurement. The blood concentration of ICG obtained by the conventional method correlates well with that obtained by pulse dye densitometry. According to a previous report,[12] in 27 patients with liver disease following ICG injection, blood ICG concentration was measured by the conventional method and pulse dye densitometry simultaneously. The blood dye concentration correlated well with the value obtained by pulse dye densitometry (correlation coefficient=0.953). The optical sensor of an ICG clearance meter (DDG-2001; Nihon Kohden Industry Co. Ltd, Tokyo, Japan) was applied to the right second finger. ICG-K was determined by measuring light transmission through the finger at 810 and 940 nm.[13] The cardiac index was measured using a dye dilution method by

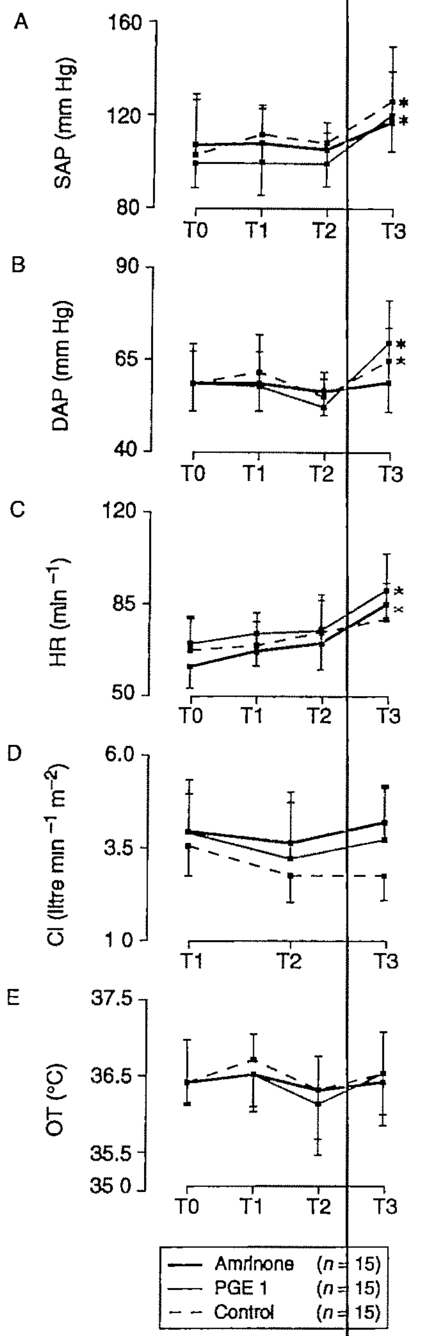

Fig 1 Changes in (A) systolic arterial pressure, (B) diastolic arterial pressure, (C) heart rate, (D) cardiac index and (E) oesophageal temperature Data are expressed as means ± SD Bold solid line, amrinone group (n=15), thin solid line, PGE$_1$ group (n=15), broken line, control group (n=15) *P<0 008 compared with the mean preoperative level, t_0, before laparotomy; t_0, just before induction of liver ischaemia. t_2, just after liver resection; t_3, 60 min after reperfusion

calculating the area under the very initial phase of the ICG concentration–time curve with a computer. Systolic and diastolic arterial pressure (SAP and DAP), heart rate and oesophageal temperature were also recorded at t_0, t_1, t_2 and t_3. The lactate concentration and base excess of arterial blood were measured with an ABL 625 analyser (Radiometer, Copenhagen, Denmark) at the same times.

The observation period was divided into three phases: the pre-ischaemic phase (from t_0 to t_1), the ischaemic phase (from t_1 to t_2) and the post-ischaemic phase (from t_2 to t_3). The rate of lactate accumulation in the pre-ischaemic phase was calculated as the difference between blood lactate concentrations at t_1 and t_0, divided by the duration of this phase. The rate of lactate accumulation in the ischaemic phase or elimination rate in the post-ischaemic phase was calculated similarly.

Blood aspartate and alanine aminotransferase (AST and ALT) concentrations were measured before surgery (day −1), one hour after surgery (day 0) and on the first and third postoperative days (days 1 and 3, respectively).

Statistical analysis

The statistical software package Stat View (SAS Institute Inc., Cary, NC, USA), version 5.0 for Windows, was used throughout the analysis. Ages are given as range (median) and all other data as means (SD). The physical and surgical characteristics of the groups were compared by the χ^2 test or an analysis of variance (ANOVA), as appropriate. Calculated variables such as the lactate accumulation rate in the groups were compared by ANOVA. Evaluated retrospectively, 15 patients in each group ensured a 75% chance of detecting a relevant difference (d=1.00) with a significance level of α=0.05 for a two-tailed test. The difference d is given by the difference between the means of two groups divided by the variance, σ.[14]

The variables measured during and after anaesthesia in each group were compared with the corresponding baseline levels using ANOVA with Bonferroni's correction. The variables measured during and after anaesthesia were analysed with a two-way ANOVA for repeated measures to examine differences among the groups. Differences were considered significant at P<0.008 in ANOVA with Bonferroni's correction and at P<0.05 in the other analyses.

Results

Surgical results

Surgery lasted for 410 (137) min (95% confidence interval (CI) 357–465 min). The pre-ischaemic and ischaemic phases lasted 165 (95) min (95% CI 131–198 min) and 70 (46) min (95% CI 57–85 min), respectively. Blood loss was 601 (390) ml kg^{-1} (95% CI 443–756 ml kg^{-1}) or 13.6 (9.1) ml kg^{-1} (95% CI 9.5–16.5 ml kg^{-1}). The resected liver weighed 157 (186) g (95% CI 95–238 g). There were no significant differences among the groups with regard to these surgical characteristics (Table 2).

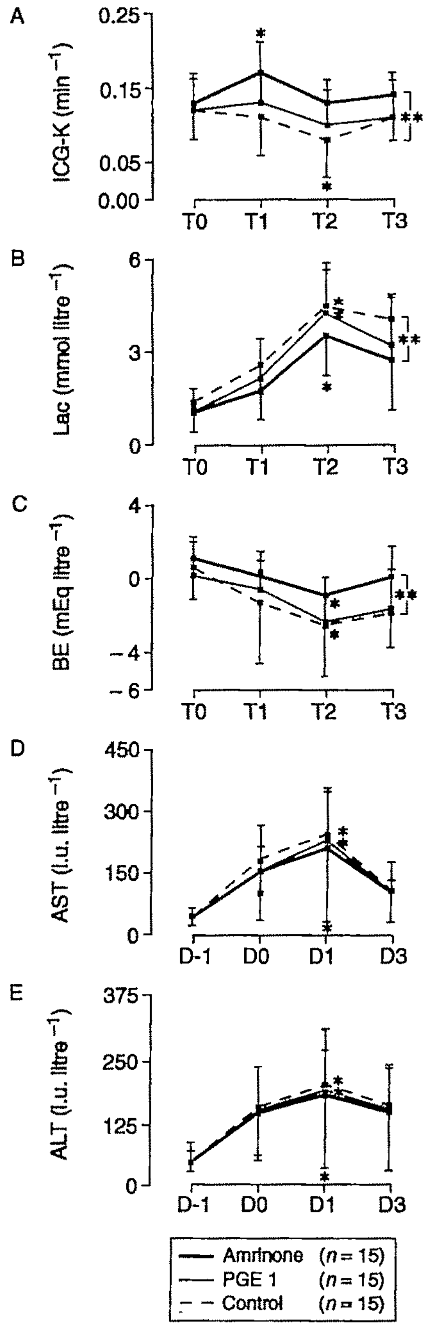

Fig 2 Changes in (A) the indocyanine green elimination rate, (B) arterial blood lactate concentration, (C) base excess, (D) plasma aspartate aminotransferase and (E) alanine aminotransferase. Data are expressed as means ± SD. Bold solid line, amrinone group (n=15); thin solid line, PGE$_1$ group (n=15), broken line, control group (n=15). *P<0.008 compared with the mean preoperative level; **P<0.05 by two-way repeated-measures ANOVA to examine the effect of PGE$_1$ or amrinone on each factor compared with controls; t_0, before laparotomy; t_1, just before induction of liver ischaemia; t_2, just after liver resection; t_3, 60 min after reperfusion, D-1, day −1 (the day before the operation); D0, day 0, 1 h after the operation; D1 and D3, the first and third postoperative days, respectively.

Table 3 Rate of lactate accumulation or elimination rate (μmol l^{-1} min^{-1}) (mean (SD)). Positive numbers indicate accumulation and negative numbers elimination. ^{a}Compared with controls

Phase	Control (n=15)	Amrinone (n=15)	PGE$_1$ (n=15)	P value^a
Pre-ischaemic	11.2 (3.8)	6.2 (3.4)	7.9 (2.6)	0.03
Ischaemic	28.8 (33.8)	32.7 (26.6)	28.3 (25.4)	0.89
Post-ischaemic	−2.8 (3.1)	−6.8 (3.5)	−6.1 (3.7)	0.09

Complications after hepatectomy were observed in one, two and two patients in the control, amrinone and PGE$_1$ groups, respectively. These included bile leakage from a dissection plane of the liver in two patients and pleural effusion in three patients. No patients died during the first 30 days after the operation.

Changes in haemodynamics

SAP and DAP did not change significantly between t_0 and t_2 in any group, but increased significantly at t_3 in the control and PGE$_1$ groups ($P<0.0001$ in each comparison, Figure 1A and B). Heart rate did not change significantly between t_0 and t_2 in any group, but was significantly higher at t_3 than at t_0 in the amrinone and PGE$_1$ groups (P=0.007 and P=0.001 in each comparison, Figure 1C). Cardiac index and oesophageal temperature remained unchanged throughout the observation period in all three groups (Figures 1D and E).

Changes in ICG-K

After drug treatment, ICG-K was significantly higher at t_1 than at t_0 (P=0.006) in the amrinone group, but not in the PGE$_1$ or control group (Figure 2A). Just after reperfusion, ICG-K was significantly lower at t_2 than at baseline in the control group (P=0.006), but not in the amrinone or PGE$_1$ groups. The ICG-K concentration at t_3 did not differ from baseline in any of the groups.

Changes in lactate and base excess

The lactate concentration tended to increase during the pre-ischaemic phase, increased markedly during the ischaemic phase and tended to decrease during the post-ischaemic phase (Figure 2B). The lactate concentration at t_2 was significantly higher than baseline in each group ($P<0.0001$ in each comparison). The rate of lactate accumulation or elimination during each phase is shown in Table 3.

Base excess continued to decline until t_2 in each group (Figure 2C). Base excess at t_2 was significantly lower than at t_0 in the PGE$_1$ and control groups (P=0.007 and P=0.003, respectively).

Changes in AST and ALT

AST concentrations in all groups reached their maximum (216 (239), 231 (152) and 246 (125) IU litre^{-1} in the amrinone, PGE$_1$ and control groups, respectively) on the first postoperative day (Figure 2D). ALT concentrations showed similar changes (Figure 2E).

Comparison among the groups

Two-way repeated-measures ANOVA revealed that SAP, DAP, heart rate, cardiac index, oesophageal temperature, AST and ALT did not differ significantly among the groups at any time in the observation period.

In contrast, ICG-K in the amrinone group differed significantly from that in the control group (P=0.03). ICG-K in the PGE$_1$ group tended to differ from those in the control and amrinone groups, but these differences were not statistically significant (P=0.1 for each comparison).

Lactate concentration and base excess in the amrinone and control groups also differed significantly throughout the observation period (P=0.04 and P=0.03, respectively). Lactate concentration and base excess in the PGE$_1$ and control groups differed, but these differences were not statistically significant (P=0.09 and P=0.25, respectively).

The lactate accumulation rate during the pre-ischaemic phase in the amrinone group was significantly lower than that in the control group (P=0.03, Table 3). In contrast, the lactate accumulation rates during the ischaemic phase were comparable in the three groups. During the post-ischaemic phase, the lactate elimination rate in the amrinone and PGE$_1$ groups tended to be lower than that in the control (P=0.09).

Discussion

To our knowledge, there have been no previous reports on the effects of amrinone on the function of liver subjected to ischaemia–reperfusion injury. This randomized, blinded study demonstrated that continuous intravenous administration of low-dose amrinone resulted in enhanced ICG-K elimination during hepatectomy. Such treatment also resulted in a reduced blood lactate concentration. With amrinone, lactate accumulation was reduced before ischaemia and its elimination tended to be greater after ischaemia. ICG elimination is a reliable indicator of hepatic blood flow and of hepatocellular function.[15 16] In addition, as we and other authors have demonstrated in previous studies,[17 18] blood lactate profiles, especially lactate accumulation and elimination rates, are some of the most sensitive indicators of hepatic function during liver surgery. The results obtained in this study indicate that low-dose amrinone augments intraoperative liver function during hepatectomy involving liver ischaemia.

How does low-dose amrinone keep ICG-K concentrations higher intraoperatively? One possible explanation is increased hepatic blood flow either through augmented cardiac function or through dilated hepatic vascular beds, although the cardiac index in the amrinone group was comparable to that in the control group. Total hepatic flow is usually regulated by hepatic arterial flow. This unique intrinsic regulation system is called the hepatic arterial buffer response.[19] The arterial buffer maintains intrahepatic pressures and liver volume.[19] However, it is possible that amrinone and isoflurane significantly attenuate this response after ischaemia–reperfusion injury.

Another possibility is that amrinone might minimize the effects of intracellular calcium overload and its harmful sequelae. Liver ischaemia–reperfusion injury is mediated, at least in part, through an elevation in intracellular calcium.[20] Amrinone is known to inhibit cytoplasmic calcium mobilization, increasing the cAMP concentration.[21]

During the pre-ischaemic phase, lactate concentration tended to increase in all three groups. This might be a result of decreased uptake of lactate resulting from decreased hepatic blood flow during compression and mobilization of the liver for hepatectomy, which caused lactate accumulation even before the liver was subjected to ischaemia.[18 22] Anaesthetic agents might also impair hepatic function. Although isoflurane does not appear to depress hepatic function, as measured by the ICG test in patients with normal hepatic function,[18] a dose-dependent decrease in hepatic blood flow induced by isoflurane might depress liver function significantly in cirrhotic patients, and thus enhance lactate accumulation.[23–26] In this pre-ischaemic phase, lactate accumulation was prevented to a considerable extent with amrinone. This result, coupled with enhanced ICG-K, indicated that amrinone augments intraoperative hepatic function during this phase.

During the ischaemic phase, lactate accumulation progressed at similar rates in all three groups. Increases in lactate concentrations during this phase result primarily from increased lactate production by tissue ischaemia and secondarily from the abolition of lactate uptake by the liver.[17 18] The similar lactate profiles in the three groups during this phase were not surprising, since hepatic blood flow is abolished completely during Pringle's manoeuvre, regardless of the drugs used. Postoperative AST and ALT concentrations were similar among the groups. This might also suggest that the magnitude of liver damage caused by ischaemia was similar irrespective of the drugs. In this respect, amrinone might not provide significant organ protection against ischaemia during this phase. Immediately after the end of ischaemia, however, ICG-K was well maintained with amrinone, while it was reduced in the control group. The lactate concentration in the amrinone group immediately after ischaemia remained lower than that in the control group. In addition, after ischaemia, lactate elimination tended to be enhanced with amrinone. These results suggest that liver function was maintained better in the amrinone group during the immediate post-ischaemic period. Thus, the possibility that amrinone provides some organ protection against ischaemia could not be excluded.

Clearance of amrinone in cirrhotic patients is not known, but is likely to be significantly reduced in these circumstances. Although 26–40% of amrinone given intravenously is excreted in the urine unchanged, a substantial fraction of the remaining dose undergoes hepatic metabolism.[27] The rate of amrinone administered by continuous infusion in the present study was fixed at 4.0 $\mu g\ kg^{-1}\ min^{-1}$, which is much less than that used for the treatment of heart failure (10–20 $\mu g\ kg^{-1}\ min^{-1}$).[28] Furthermore, in the present protocol, a loading dose was not given, which is usually a bolus of 1–2 $mg\ kg^{-1}$.[28] The effects of amrinone on ICG metabolism might differ if a different amrinone administration protocol was used, and this might throw further light on this subject.[29]

In the PGE_1 group, ICG-K concentrations tended to remain higher during surgery. This suggests that PGE_1 may have some beneficial effects on intraoperative liver function. However, this effect was no greater than that of amrinone. Our results with PGE_1 were comparable to those of Tsukada and colleagues,[30] who demonstrated that ICG elimination was enhanced by PGE_1 dose-dependently in doses ranging from 0.01 to 0.05 $\mu g\ kg^{-1}\ min^{-1}$ in cirrhotic patients undergoing partial liver resection. Another study[29] revealed that continuous intravenous administration of low-dose PGE_1 (0.02 $\mu g\ kg^{-1}\ min^{-1}$) had favourable pharmacological effects on the liver during the postoperative period in cirrhotic patients who had undergone subsegmentectomy of the liver.

In conclusion, low-dose amrinone enhanced ICG elimination and lactate metabolism during hepatic resection in cirrhotic patients; its detailed mechanism of action remains unclear.

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Blood propofol concentration and psychomotor effects on driving skills

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We studied psychomotor performance in 10 healthy volunteers during recovery after a target-controlled infusion of propofol. Choice reaction time, dual task tracking with secondary reaction time and a within-list recognition task were assessed at target blood propofol concentrations of 0.8, 0.4 and 0.2 μg ml^{-1}. Performance was impaired most at the highest blood propofol concentration (choice reaction time increased by a mean of 247 ms and secondary reaction time by a mean of 178 ms). Choice reaction time and dual task tracking with secondary reaction time were the most sensitive and reliable methods of assessment (significant difference from baseline ($P<0.05$) at a propofol concentration of 0.2 μg ml^{-1} with choice and secondary reaction time testing). Within-list recognition assessment of memory was not sufficiently sensitive at very low propofol concentrations. The impairment in choice and secondary reaction time with a blood propofol concentration of 0.2 μg ml^{-1} was less than that observed with a blood alcohol concentration of 50 mg 100 ml^{-1} and no greater than that observed with a blood alcohol concentration of 20 mg 100 ml^{-1} in a previous study involving healthy volunteers.

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With the development of new shorter-acting anaesthetic and analgesic drugs, the recovery of psychomotor function and fitness to operate a motor vehicle after day-case anaesthesia have become important issues. There is ample experimental evidence that function is impaired after anaesthesia. For example, Whitehead and co-workers[1] have shown a dose-related impairment by propofol of choice reaction time. Dose-related impairment has also been reported with older anaesthetic agents such as thiopental.[2]

Although it is possible to show that skills related to those required while driving are impaired, the criteria to be used in establishing whether a patient is fit to drive have not been established. Our previous study, which examined the relationship between blood alcohol concentration (BAC) and psychomotor effects,[3] attempted to provide a standard by suggesting that the maximum permitted BACs for driving in three European countries (20, 50 and 80 mg 100 ml^{-1}) be used as reference points with which recovery from different anaesthetic techniques could be compared.

Propofol was chosen for this study because of its frequent use during day surgery. In this prospective cohort study, psychomotor function and memory were assessed in volunteers during recovery after a target-controlled infusion of propofol using the Diprifusor target-controlled infusion system. Assessments were made using tests of choice reaction time, tracking with secondary reaction time and within-list recognition.

Methods

After obtaining approval from the ethics committee and written informed consent, 10 healthy volunteers were studied (nine male and one female; mean age 32 yr, range 23–40 yr; mean body weight 75.5 kg, range 57–86 kg). The subjects were informed that they would be deeply sedated using propofol administered via the Diprifusor and would slowly recover consciousness in a stepwise fashion. They were also told that, during the recovery period, they would be asked to repeat psychomotor tests.

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Subjects with a history of cardiac, pulmonary, neurological, hepatic or renal disease, psychiatric disorder or substance misuse were excluded. Subjects were instructed not to eat for 6 h or drink for 4 h before the study nor to drive a car or operate any machinery in the evening after the study. All subjects were driven home and were accompanied by a competent carer that evening.

Assessments took place during working hours in a laboratory in the Department of Anaesthesia, and lasted approximately 4 h. An intravenous cannula was inserted in the dorsum of the non-dominant hand. Full continuous monitoring, consisting of ECG, non-invasive arterial pressure and peripheral arterial oxygen saturation (Sp_{O_2}), was instituted. The volunteers then repeated the psychomotor tests to reduce practice effects and to establish a performance baseline. All subjects received a target-controlled infusion of propofol using the 'Diprifusor' target-controlled infusion system which was increased until the subjects were deeply sedated. A minimum score of 6 using the modified Steward coma scale[4] (Table 1) was used as the criterion for the endpoint of sedation. The propofol concentration was then reduced to a target of 0.8 μg ml^{-1}, maintained at that concentration for 30 min, then reduced to targets of 0.4 and 0.2 μg ml^{-1} for 30 min each. Supplemental oxygen was administered via nasal prongs if the oxygen saturation dropped below 96%. All three assessments of psychomotor performance were carried out three times each over the 30 min periods when the target blood propofol concentration was 0.8, 0.4 and 0.2 μg ml^{-1}. This gave a total of 10 assessments for each test, including baseline measurements. At the end of the study period the propofol infusion was discontinued and the patients recovered in the Department until fit enough to be escorted home.

Subjects performed two psychomotor tests and one memory test during the period of the study. Computerized tasks[5] to measure choice reaction time, and dual-task tracking and secondary reaction time were chosen for their known sensitivity to the sedative effects of anaesthetics and alcohol[6 7] and had been shown to be sensitive in our previous study.[3] Within-list recognition memory has been shown sensitive to sedative effects[8] and, as memory is a central component of cognitive competence, was therefore included to extend the range of the test battery.

Primary tracking and secondary visual reaction time

Subjects operated a computer mouse to control an on-screen icon (a cross) with the task of maintaining it in contact with a 'target' circle moving at varying velocity and direction across the screen of a visual display unit (VDU). The primary task score was the time spent 'on target' (i.e. the proportion of the total time spent tracking during which the cross was kept in contact with the circle) expressed as the root mean square error (r.m.s.). While performing the tracking test, subjects had also to respond by pressing the keyboard spacebar when visual signals (star-shaped icons) appeared unpredictably in the periphery of the VDU. Secondary task performance was recorded in milliseconds.

Choice reaction time

Five numbered circles were displayed on the VDU, corresponding spatially to response keys 1–5 on the adjoining keyboard. During each trial, the subject's dominant hand rested on the keyboard spacebar. After a variable interval, one of the circles randomly changed colour, requiring the subject to lift their hand from the spacebar and press the appropriate response key. Reaction time was expressed in milliseconds and consisted of two components; 'decision time' (time taken to lift hand from the spacebar) and 'movement time' (time taken to move to the response key).

Within-list recognition

Subjects were presented with lists of 23 words, spoken at a rate of one word every 2 s. Seven of the words in each list were each repeated once at some point in the list; the subjects' task was to detect these repetitions. By varying the number of words occurring between the repeated words, the detection task also becomes one of memory retention. Previous research has shown that the probability of detecting a repetition declines as the number of intervening words increases; this effect is particularly evident in sedated subjects, suggesting that encoding and retrieval processes are impaired. The number of words intervening between the repetitions of the 'target' words was 0, 1, 2, 4, 8 or 16. The

Table 1 Modified Steward coma scale

Consciousness	4	fully awake, eyes open; conversive
	3	lightly asleep; eyes open intermittently
	2	eyes opened on command or in response to name
	1	responds to ear pinching
	0	does not respond
Airway	3	opens mouth and/or coughs on command
	2	no voluntary coughing but clear unsupported airway
	1	airway obstructed on neck flexion, but clear on extension unsupported
	0	airway obstructed without support
Activity	2	raises one arm on command
	1	no purposeful movement
	0	not moving

subjects responded to repeated words by raising their thumb. Two lists were presented in each test period.

Data were analysed with balanced analysis of variance using Minitab software version 10. Significant main effects were investigated further by pairwise comparisons of means using *t*-tests and Bonferroni corrections as appropriate. Within-list recognition data were analysed by non-parametric tests. All-alpha levels were two-tailed; those less than 0.05 were considered to indicate statistical significance.

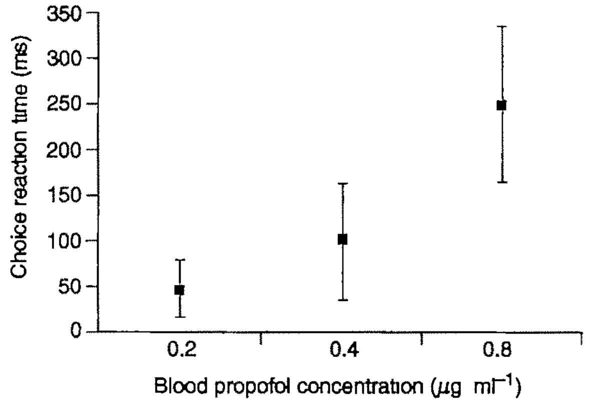

Fig 1 Mean (5–95% confidence interval) increase in choice reaction time, in milliseconds, recorded at blood propofol concentrations of 0.2, 0.4 and 0.8 $\mu g\ ml^{-1}$.

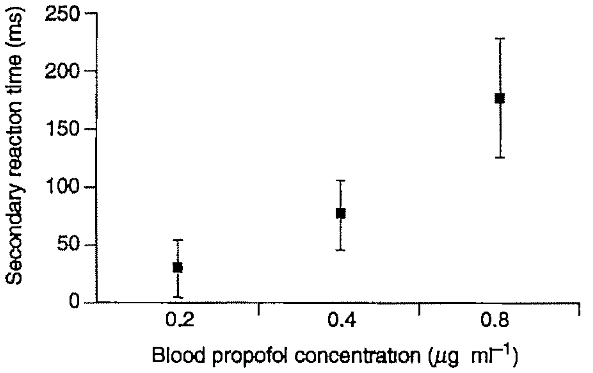

Fig 2 Mean (5–95% confidence interval) increase in secondary reaction time, in milliseconds, recorded at blood propofol concentrations of 0.2, 0.4 and 0.8 $\mu g\ ml^{-1}$.

Results

The maximum target blood propofol concentration required to sedate the subjects to the required level of a modified Steward coma score of <6 varied from 1.4 $\mu g\ ml^{-1}$ to 3.0 $\mu g\ ml^{-1}$. At maximum sedation level, all subjects maintained their airway. No subject required supplemental oxygen for a fall of oxygen saturation below 96%.

Psychomotor testing

Choice reaction time

Figure 1 illustrates the statistically significant ($P<0.01$) increase in choice reaction time as blood propofol concentration increased. Comparison of means by *t*-test showed that reaction times at all propofol concentrations were significantly longer than at baseline, and also significantly longer at 0.8 $\mu g\ ml^{-1}$ than at 0.4 $\mu g\ ml^{-1}$.

Dual task performance

(i) Secondary visual reaction time. Figure 2 shows the statistically significant effect of propofol concentration ($P<0.01$) reflected in the increase in secondary reaction time as blood propofol concentration increased. *t*-Tests confirm that reaction time was significantly longer at all blood propofol concentrations than at baseline, and that all pairwise comparisons between concentrations were also significant (Table 2). (ii) Tracking. Figure 3 illustrates the deterioration in tracking performance seen with increasing blood propofol concentration ($P<0.01$). There was a significant difference between the 0.8 $\mu g\ ml^{-1}$ propofol group and baseline and also between the 0.2 and 0.8 $\mu g\ ml^{-1}$ groups (Table 2).

Within-list recognition performance

The greatest deterioration in recognition performance occurred with the highest blood propofol concentration, 0.8 $\mu g\ ml^{-1}$ (Figure 4). The effect was not, however, significant. There was not always a detectable deterioration in performance at the lower blood propofol concentration. With a blood propofol concentration of 0.4 $\mu g\ ml^{-1}$, the recognition performance was better than baseline when the repeated words were 4, 8 or 16 words apart. At a blood propofol concentration of 0.2 $\mu g\ ml^{-1}$, the performance was better than baseline at the 8 and 16 word intervals.

Table 2 Deterioration in performance observed with choice reaction time (CRT), secondary reaction time (SRT) and tracking at the three propofol concentrations tested *Significantly different from baseline ($P<0.05$). **Significantly different from baseline and from 0.2 and 0.4 $\mu g\ ml^{-1}$ groups ($P<0.05$)

Propofol concentration ($\mu g\ ml^{-1}$)	**Mean (95% CI) deterioration in**		
	CRT (ms^{-1})	**SRT (ms^{-1})**	**Tracking (%)**
0.2	46 (15–77)*	29 (4–53)	2.5 (−2 to −7)
0.4	97 (33–160)*	76 (46–105)*	−3.5 (−8.5 to 1.5)
0.8	247 (162–332)**	178 (127–229)**	−19 (−27 to −12)**

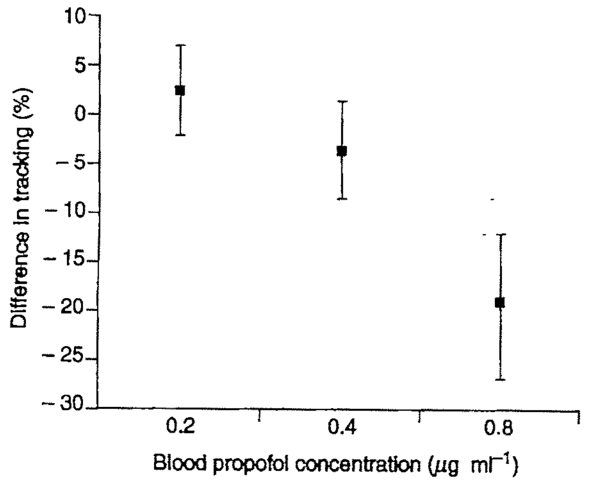

Fig 3 Change in tracking performance (expressed as a percentage) with increasing blood propofol concentration.

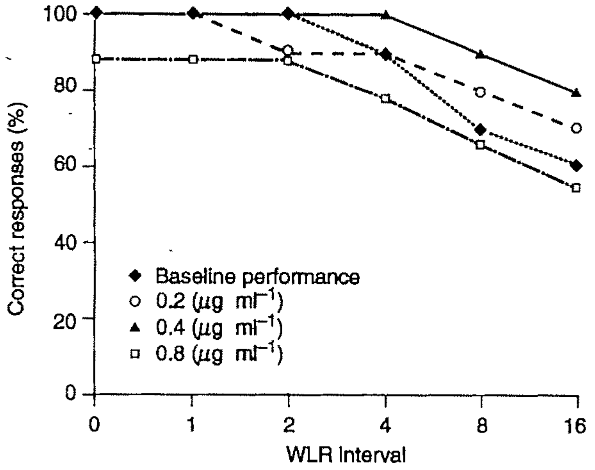

Fig 4 Within-list recognition (WLR) score (median) expressed as a percentage of correct responses at baseline (◆) and with three different blood propofol concentrations, 0.2 (○), 0.4 (▲) and 0.8 μg ml^{-1} (□).

Discussion

We have examined the relationship between blood propofol concentration and psychomotor performance in healthy volunteers using a decreasing concentration of blood propofol to simulate the decreasing concentrations that would be seen during recovery from anaesthesia. The findings of this study show that choice reaction time and dual task tracking with secondary reaction time provide sensitive assessments of progressive performance impairment with increasing blood concentrations of propofol.

In contrast, within-list recognition did not discriminate significantly between propofol concentrations. The fact that memory performance at low concentrations of propofol was, on occasion, better than at baseline might suggest an unresolved practice effect. Equally, however, it might also reflect better concentration in the lightly sedated state because of reduced distractibility.

Common criticisms of psychomotor tests are that they often lack sensitivity and validity and that there are no well-defined 'gold-standard' tests with normative databases to define criteria for impaired performance. Such criticisms are well founded but, none the less, the present results indicate that, even at low blood propofol concentrations, choice reaction time and a dual task are sensitive to quite subtle impairment. Furthermore, although such tests are 'artificial', they do reflect critical aspects of skills required when driving and are sensitive to sedative effects in the context of real-life environments requiring skilled performance.[9]

The question of a meaningful standard against which to compare performance impairment has been addressed by Tiplady[10] and by our recent empirical work.[3] Tiplady has noted that dose-related effects of alcohol upon psychomotor performance are reasonably well established and has described the consequent potential value of alcohol as a comparator to assess the effects of anaesthetic agents. He has also noted the virtue that BACs are set as arbitrary threshold standards for fitness versus non-fitness to drive. Using the present psychomotor tests, we have previously assessed impairment at BACs reflecting three current European drink-driving limits (20, 50 and 80 mg 100 ml^{-1}). The impairment found with propofol 0.2 μg ml^{-1}, the lowest dose used in the present study, was comparable to that measured at 20 mg 100 ml^{-1} BAC in our previous experiment. The latter BAC is equivalent to the Swedish drink driving limit and marks evidence for impairment at a considerably lower BAC than the limit of 80 mg 100 ml^{-1} set in the UK. On the basis of such experimental results, one might therefore generalize and conclude that affected individuals may be vulnerable to mishap in real-life situations. Tiplady, however, provides the important caveat that test performance 'cannot be validated in a strict sense against the likelihood of road accidents (or of accidents at home, for that matter)' (reference 10, p. 33).

Given sufficiently sensitive testing conditions and appropriate tests, impairment of mental abilities can be demonstrated for four or more post-operative days.[11] The question remains open as to whether driving after receiving an anaesthetic should be banned until psychomotor performance on all tests has returned to normal. It could be argued that a small degree of impairment, similar to that seen with a BAC of 20 mg 100 ml^{-1} (or propofol 0.2 μg ml^{-1} in volunteers), would be acceptable in drivers. The impairment in psychomotor performance found at this concentration must be compared with that measured in patients receiving, for example, tricyclic antidepressants, antihistamine agents for hay fever or analgesics for back pain. This is obviously an issue that will need full and widespread debate within the profession, but is of growing importance with an expanding and increasingly mobile day-case population.

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Blood alcohol concentration and psychomotor effects

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This study assessed the effect of intravenous alcohol infusions on psychomotor impairment and compared it with that of alcohol administered orally. Comparisons were made between three European drink-driving limits of blood alcohol concentration (BAC) (20, 50 and 80 mg 100 ml^{-1}) and an oral dose of alcohol 0.75 mg kg^{-1}. Twelve volunteers, aged 22–34 yr, were recruited. At targets of 20, 50 and and 80 mg 100 ml^{-1}, the mean (SD) BAC was 22.1 (3.7), 51.5 (3.3) and 80.5 (4.2) mg 100 ml^{-1}, respectively. The peak BAC following an oral dose of alcohol 0.75 mg kg^{-1} ranged from 19 to 68 mg 100 ml^{-1}. In psychomotor testing, choice reaction time deteriorated with increasing BAC and showed significant differences between baseline and the 50 ($P<0.05$) and 80 mg 100 ml^{-1} ($P<0.01$) conditions. Dual-task secondary reaction time deteriorated with increasing BAC and showed a statistically significant difference between all groups and baseline (oral and 20 mg groups, $P<0.05$; 50 and 80 mg groups, $P<0.01$). Dual-task tracking in the 50 and 80 mg groups was significantly different from baseline ($P<0.05$ and $P<0.01$, respectively). Oral dosing resulted in widely variable BACs, making it difficult to assess psychomotor impairment reliably. An intravenous infusion enables the BAC to be maintained within a narrow range. This allows precision when investigating the effects of alcohol on psychomotor performance.

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Post-operative psychomotor performance is commonly assessed in anaesthetic research when studying recovery from general anaesthesia, and includes assessment of fitness to drive. One of the difficulties encountered when making such assessments is the fact there is no standard against which to compare evidence of performance impairment. It is, therefore, difficult to define the minimally acceptable degree of postoperative impairment and to determine how soon it is safe to drive after a general anaesthetic for a day surgery procedure.

The World Health Organization previously recommended that the behavioural effects of drugs be compared with those of alcohol.[1] The logic of such an approach is that degrees of performance impairment have been established for levels of various blood alcohol concentration (BAC) with subsequent implications for supposed 'fitness to drive'. Thus, where recovery from an anaesthetic drug is associated with performance impairment similar to, or greater than, that seen with a given BAC, there may be grounds for concluding that the impairment would have real-life consequences. Governments, however, vary in legislation regarding permitted BACs when driving, with the result that there are different legal 'limits' around the European Union: for example, BACs of 20, 50 and 80 mg 100 ml^{-1} in Sweden, France and the UK, respectively. These values were used in the present study as the target points at which psychomotor impairment would be assessed.

The effects of blood alcohol on tasks that simulate driving skills have been studied widely.[2–4] Typically, the method involves administering an oral dose of alcohol and then assessing the behavioural changes produced. Oral doses of alcohol can, however, produce considerable variability in pharmacokinetic variables such as the peak BAC, the time to achieve peak concentration and the time course of decay in blood concentration, because of differing bioavailability.[5–7] Moreover, as psychometric assessment of alcohol-

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induced impairment is conducted in a dynamic situation where the alcohol concentration is increasing or decreasing, it can be difficult to compare results of assessments which follow one another.

The present study was designed to assess psychomotor impairment during intravenous administration of alcohol compared with oral dosing. We administered alcohol first by the conventional single oral dose and then by the intravenous route to maintain a steady BAC. The effects of BAC on the skills required in driving were assessed by two psychomotor tests.

Methods

Subjects

Following local ethics committee approval, 12 healthy volunteers (nine male, three female; mean (range) age 30 (22–34) yr; mean (range) weight 76.5 (58–86.5) kg) participated in the study after giving informed written consent. Their history of alcohol use was moderate (range 3–35 units per week). A full medical history was taken and any volunteer with a history of cardiac, pulmonary, neurological, hepatic or renal disease, psychiatric disorder or substance misuse was excluded. Subjects were instructed not to eat or drink for 4 h before the study nor to drive a car or operate any heavy machinery the evening after the study. Subjects were informed that they would receive a volume of alcohol to drink, followed by an alcohol infusion, and that the maximum blood alcohol level would not exceed the maximum permitted BAC for driving in the UK. All subjects were driven home after the study.

Assessments took place in a laboratory in the Department of Anaesthesia and lasted approximately 5 h. The subject and at least one investigator were present for each session. On arrival, two intravenous cannulae were inserted, one in each arm. One cannula was used for blood sampling and the other for administering intravenous alcohol. The alcohol analyser (Lion Alcolmeter; Lion Laboratories Ltd, Barry, UK) was calibrated according to the manufacturer's instructions. Breath analysis of blood alcohol was used to confirm that the volunteers had abstained from alcohol as required. The 12 volunteers then repeatedly performed the psychomotor tests to reduce any discernible practice effect and to establish a set performance baseline. Subjects were unaware of the dose of alcohol consumed. All received an initial single oral dose of alcohol 0.75 g kg^{-1} (of 40% vodka) diluted up to a volume of 350 ml in fresh orange juice and consumed over 15 min. Breath analysis of BAC was then performed at 3 min intervals until a plateau was reached. This was recorded as the peak. This produced a large spread of peak BAC, from 19 to 68 mg 100 ml^{-1}. When the peak BAC had been achieved, the subject was asked to perform a set of psychometric tests. After completion of the psychomotor tests, breath analysis of BAC was performed every 3 min during the fall in BAC. When the BAC had decreased to approximately 20 mg 100 ml^{-1}, as measured by breath analysis, an intravenous infusion of alcohol (5% in 0.9% saline solution) was commenced.

The rate of infusion of alcohol was altered by the investigator in response to the measured BAC displayed on the breath analyser. The aim was to maintain the BAC steady at a concentration of 20 mg 100 ml^{-1}, then at 50 mg 100 ml^{-1} and finally at 80 mg 100 ml^{-1} for 30 min each. The BAC was analysed using the breath analyser as frequently as required (approximately every 3 min) until a steady-state BAC was achieved and then measured before and after each set of psychometric tests. Once a subject's BAC had reached a stable value of 50 mg 100 ml^{-1}, they were asked whether they would feel capable of driving a car safely if required to do so in the event of an emergency. During the experiments, the subjects had one or more blood samples taken to assess the correlation between the breath-assessed BAC measured by the Alcolmeter and the blood-assessed concentration measured using a liquid phase chromatographic technique. The subjects relaxed between psychometric assessments by reading or listening to the radio.

Psychomotor testing

Subjects repeated two psychomotor tests on a personal computer. Computerized tasks[8] of dual-task tracking and secondary reaction time and choice reaction time were chosen for their known sensitivity to the sedative effects of alcohol and other drugs.[9] [10] The tests were performed before alcohol administration, then at the peak BAC after the oral dose, and then repeated three times each at 15 min intervals at 20, 50 and 80 mg 100 ml^{-1}. This gave a total of 11 sets of psychomotor test data for each subject including the baseline assessment.

Primary tracking and secondary visual reaction time

Subjects operated a computer mouse to control an on-screen icon (a cross) with the task of maintaining it in contact with a 'target' circle moving at varying velocity and direction across the screen of a visual display unit (VDU). The primary task score was the time spent 'on target' (i.e. the proportion of total time spent tracking during which the cross was kept in contact with the circle) expressed as the root mean square error (r.m.s.). While performing the tracking test, subjects had also to respond by pressing the keyboard spacebar when visual signals (star-shaped icons) appeared unpredictably at the edges of the VDU. Secondary task performance was recorded in milliseconds.[11]

Choice reaction time

Five numbered circles were displayed on the VDU, each corresponding spatially to response keys '1' to '5' on the adjoining keyboard. During each trial, the subject's dominant hand rested on the keyboard spacebar. After a variable interval, one of the circles randomly changed colour, requiring the subject to remove their hand from the spacebar and press the appropriate response key. Reaction time was expressed in milliseconds as 'decision time' (time taken to lift the hand off the spacebar) and 'movement time' (move to the response key).[12]

Data were stored and analysed using Minitab software version 10. The prediction error and absolute prediction error were calculated to display the relationship between the predicted BAC as measured by breath analysis and the measured BAC.[13] An underestimate of the measured BAC by breath analysis was defined as a positive prediction error. An overestimate of the measured BAC by breath analysis was defined as a negative prediction error. Bias and precision were also calculated. A positive bias was defined as an underestimate of the measured BAC by breath analysis. Psychomotor performance was expressed as a mean change from baseline for each condition. The repeated-measures design was subjected to balanced analysis of variance. Significant main effects were investigated further by pairwise comparison of means using t-test, and Bonferroni correction as appropriate. All-alpha values were two-tailed and those <0.05 were considered to indicate statistical significance.

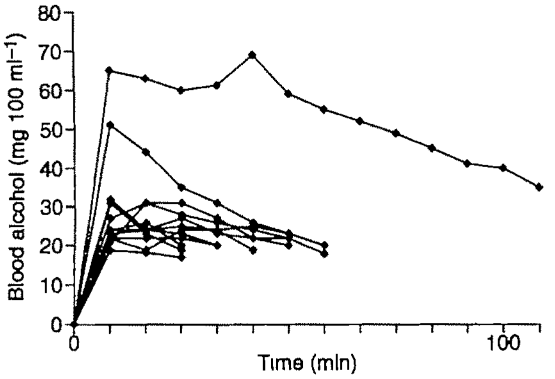

Fig 1 Variability of peak breath estimated blood alcohol concentration and subsequent decay in 12 volunteers after administration of a standard, oral dose (0.75 ml kg^{-1}).

Results

Blood alcohol concentration

Conventional single oral dose

Twenty minutes after oral consumption of alcohol, the mean (SD) peak breath alcohol concentration was 32 (14) mg 100 ml^{-1} with a range from 19 to 68 mg 100 ml^{-1}. The time for the oral dose to decay to an estimated BAC of 20 mg 100 ml^{-1} also showed marked variation, from 35 to >100 min (Figure 1).

Intravenous infusion technique

At the 20, 50 and 80 mg 100 ml^{-1} targets, the mean (SD) BAC was 22 (4), 52 (3) and 81 (4) mg 100 ml^{-1} (Figure 2).

There was a close correlation between the measured BAC and the breath-predicted values (r=0.84), but there was a general tendency for the breath to underestimate the blood concentration (Figure 3). The bias at 50 mg 100 ml^{-1} was 8.6% with a precision of 8.7%; at 80 mg 100 ml^{-1}, the bias was 22.8% with a precision of 22%. The individual subject precision error and the mean absolute prediction error increased progressively with greater BACs.

Psychomotor testing

Results of the choice reaction time task and the dual-task showed the expected wide variation between subjects (expression of performance as a change from baseline reduces such variation).[14] No significant differences were observed within subjects in choice reaction time or in primary tracking with secondary visual reaction during

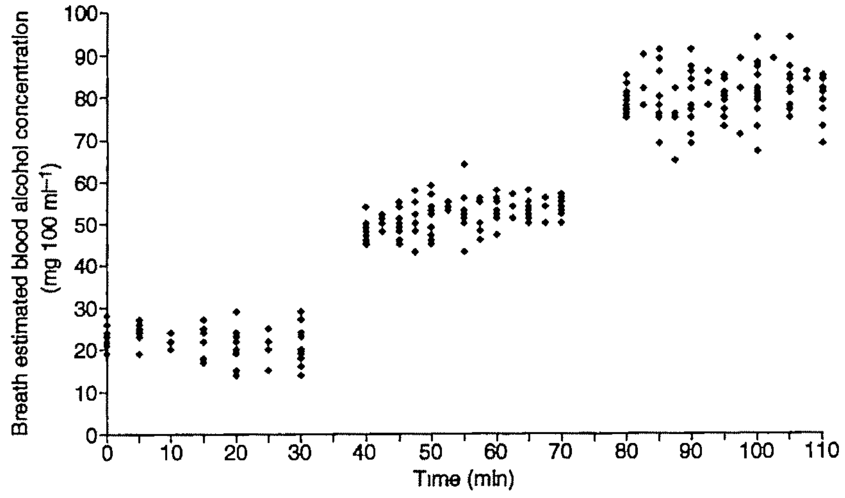

Fig 2 Variability of breath-estimated blood alcohol concentration in 12 volunteers after administration of continuous intravenous infusions to maintain target blood concentrations of 20, 50 and 80 mg 100 ml^{-1}

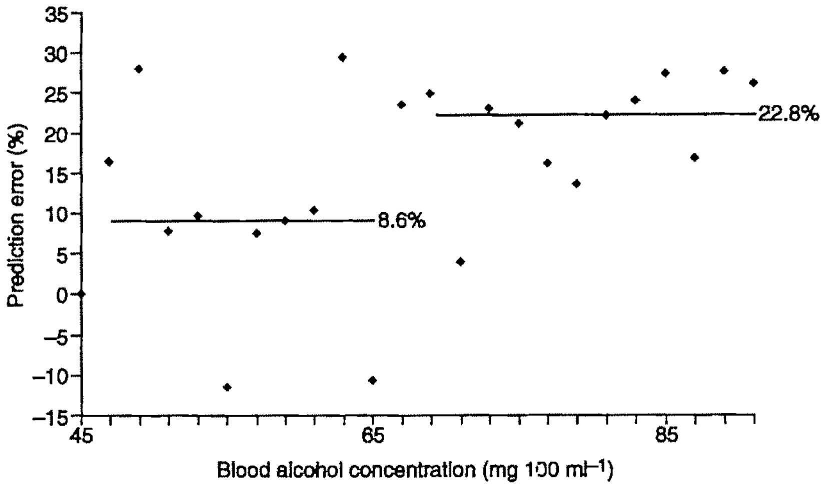

Fig 3 Prediction error of breath-estimated blood alcohol concentration (%) at various directly measured blood alcohol concentrations between 45 and 90 mg 100 ml^{-1}. An underestimate of blood alcohol concentration by the breath estimate is expressed as a positive prediction error Mean prediction errors at 50 and 80 mg 100 ml^{-1} target concentrations are displayed as solid lines

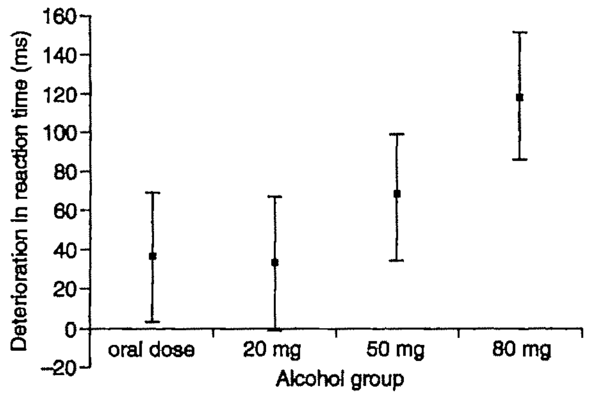

Fig 4 Deterioration in choice reaction time recorded in milliseconds in 12 volunteers with increasing blood alcohol concentration. Values are means (5–95% confidence interval). Alcohol groups: oral dose, maximum blood concentration following the oral dose, '20 mg', '50 mg' and '80 mg' are target concentrations of 20, 50 and 80 mg 100 ml^{-1}, respectively

repeat testing over the 30 min periods when the BAC remained steady.

Choice reaction time

There was a significant increase (P<0.01) in choice reaction time as BAC increased (Figure 4). Further analysis confirmed that there was a significant difference between the 50 and 80 mg responses compared with baseline (P<0.05) (Table 1).

Dual-task performance

Secondary visual reaction time

As BAC increased, secondary reaction time performance deteriorated significantly (P<0.01; see Figure 5). There was a significant difference between all alcohol concentrations and baseline and between 20 mg and 50 and 80 mg (P<0.05) (Table 1).

Tracking

Tracking performance deteriorated significantly with increasing BAC (P<0.01; Figure 6). This deterioration was significant between the 50 and 80 mg alcohol conditions and baseline, and between the 20 and 80 mg conditions (P<0.05).

In the subjective assessment of fitness to drive at 50 mg 100 ml^{-1}, all subjects felt that their psychomotor performance was affected at this BAC and stated that they felt incapable of driving a car even in the event of an emergency.

Discussion

The use of alcohol as a comparator or benchmark for other drugs has been recommended by the World Health Organization,[1] and various studies have applied the concept,[15–18] but, with conventional oral administration, achieved a variety of BACs. Thus the matter of establishing any 'standard' criteria for impairment is complex. Nonetheless, Tiplady[19] has described the potential value of alcohol as a comparator to assess the effects of anaesthetic agents (although with several important caveats) in that its dose-related effects upon psychomotor performance are reasonably well established. There is also the virtue that BACs are set as (arbitrary) threshold standards for fitness/non-fitness to drive. It is, however, one thing to show equivalence in 'impairment' but another to establish whether the degree and nature of the impairment are of clinical or practical significance. Tiplady has noted that test performance 'cannot be validated in a strict sense against the likelihood of road accidents (or of accidents at home or at work, for that matter)' (ref. 19, p.33). We would agree that alcohol is a useful comparator and that the legal reference points of 20, 50 and 80 mg 100 ml^{-1} BAC have

Table 1 Deterioration in performance with choice reaction time (CRT), secondary reaction time (SRT) and tracking at different blood alcohol concentrations *Significantly different from baseline and from blood alcohol concentration of 20 mg 100 ml^{-1} ($P<0.01$)

	CRT (ms^{-1})	SRT (ms^{-1})	Mean deterioration (95% CI) Tracking (%)
Oral dose	36 (3–69)*	31 (11–57)*	–1 (–3 to 1.0)
20 mg 100 ml^{-1}	33 (–1 to 67)	35 (16–56)*	–1.5 (–3.6 to 0.6)
80 mg 100 ml^{-1}	68 (34–99)*	86 (66–106)**	–3.2 (–5.2 to –1.13)*
100 mg 100 ml^{-1}	118 (86–151)**	120 (100–140)**	–7.8 (–9.8 to –5.8)**

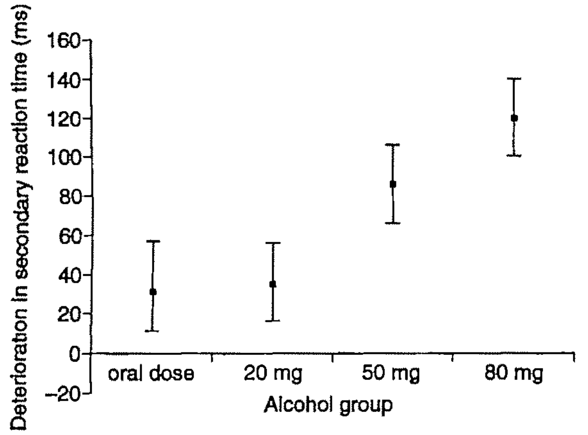

Fig 5 Deterioration in secondary reaction time recorded in milliseconds in 12 volunteers with increasing blood alcohol concentration. Values are mean (5–95% confidence interval) Key as in Figure 4

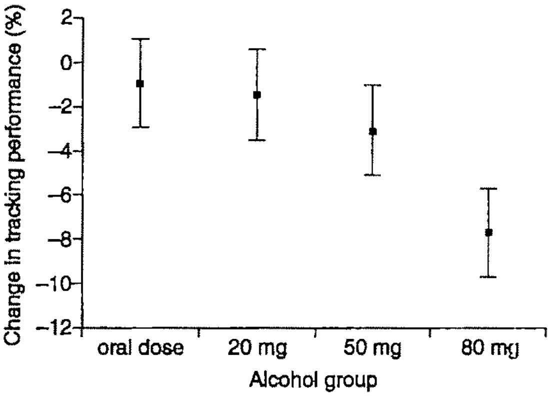

Fig 6 Deterioration in tracking performance recorded as a percentage of time on target in 12 volunteers with increasing blood alcohol concentration. Values are mean (5–95% confidence interval. Key as in Figure 4.

merit as standards against which recovery from anaesthesia or any other psychoactive drugs can be compared. This could help standardize further research and allow valid comparisons to be made between future studies.

In the present study, after oral dosing, there was considerable variability in the peak BAC achieved and in its rate of decay (Figure 1). This pharmacokinetic variability can be reduced using a continuous intravenous infusion. We demonstrated that it was possible to maintain a steady BAC for a prolonged period of time in an individual by using an intravenous infusion. Moreover, with continuous infusions, the concentration could be adjusted easily to the values required for a comparative investigation between different BACs. By maintaining BACs within narrow ranges, we demonstrated the effect of changes in BAC on psychomotor performance. The use of a breath Alcolmeter as a guide to adjust infusion rates allowed compensation for variations in individual pharmacokinetics and constant BACs to be achieved.

The difference between the breath-estimated and blood-measured BACs was greater at higher concentrations. A difference between breath-estimated BAC and blood sample BAC was also observed by Jones and Andersson.[20] The blood and breath alcohol estimates in their study were simultaneously taken from suspected 'drunk drivers' stopped for motor vehicle offences. These authors concluded that bias could be caused by a variety of factors, including the calculation used by manufacturers to correct for the blood:breath ratio, and metabolism of alcohol within the blood samples over time. The present study used a continuous infusion. This itself could result in a difference between breath and blood estimates. Davidson and co-workers[21] reported differences between estimated pharmacokinetic propofol concentrations and measured serum concentrations. This difference was decreased by temporarily stopping the infusion during the blood-sampling period. Davidson and colleagues concluded that the bias observed could be the result of constant addition to the vascular compartment by the propofol infusion. This could also hold true for the alcohol infusions used in this study.

The psychomotor tests employed in this study have previously been shown to be sensitive to the effects of psychoactive drugs such as sedatives, alcohol and anaesthetics.[22 23] Moreover, the present results replicate the impairment of performance by alcohol seen in previous studies,[9 24] including our recent work, with implications for real-life highly skilled performance.[25] The results confirm that oral administration and infusion of alcohol have similar effects on the results of the psychomotor tests. The validity of performance tests, particularly with respect to driving, has been discussed widely. While, as Tiplady has observed, the tests cannot be validated against the likelihood of road accidents, they do have content, criterion and face validity. Normative data for these tests are available with reference to previous published work.[8 25] The tasks have face validity in that they do reflect the requirements of real-life skills such as driving.[26]

Previous, important performance studies by Thapar and co-workers[15 17] and Liguori and colleagues[3] used oral doses of alcohol; performance rose and fell with inevitable changes in BAC. Thapar and co-workers used only peak BAC as their steady-state reference point, hence providing a rather narrow window of observation and consequently a small number of data points. In addition, Thapar and colleagues achieved an average peak BAC of 110 mg 100 ml^{-1}. This BAC is substantially higher than that of any European drink-driving limit. Thapar and co-workers concede that the impairment detected at a BAC of 110 mg 100 ml^{-1} is probably too high to use as a valid comparator in assessing recovery from anaesthesia. During subjective assessment in the present study, subjects felt unable to drive safely at a BAC of only 50 mg 100 ml^{-1} and dual-task assessment of secondary reaction time revealed a statistically significant difference from baseline performance a BAC of only 20 mg 100 ml^{-1}.

The maximum performance impairment in the present study occurred at a target BAC of 80 mg 100 ml^{-1}. A mean increase of 120 ms^{-1} was found for both the choice and secondary reaction times at this BAC. If this result was translated into driving a vehicle, the increase in braking distance would be some 4 m while travelling at 70 m.p.h. (112 km h^{-1}). The volunteers' subjective assessment of their impairment was that they would be incapable of driving safely at a BAC of 50 mg 100 ml^{-1}, and this was confirmed by the objective psychomotor tests. Our results contribute to the increasing literature that supports the British Medical Association's recommendation that the UK permitted BAC for driving be reduced to 50 mg 100 ml^{-1}.

We believe that we have demonstrated that it is possible to achieve greater control of chosen BACs, and subsequently to measure more precisely the degree of performance impairment, by using the intravenous administration technique. This will allow investigators to compare with greater accuracy the impairment caused by alcohol and other drugs in future.

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Continuous propofol anaesthesia for patients with myotonic dystrophy

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Myotonic dystrophy, a rare genetic disorder, may pose a serious problem to the anaesthesiologist due to muscular and extramuscular involvement. Thirteen patients, median age 21 yr were anaesthetized by continuous propofol infusion, fentanyl, atracurium and N_2O to evaluate this combination in myotonic dystrophy. Intraoperatively, neither exaggerated reactions nor haemodynamic instability was observed. Recovery was smooth and quick. Although there was a significant decrease in mean postoperative vital capacity (965 (349) ml) from the preoperative value (1664 (566) ml, P=0.0028), there was no change in mean postoperative Sp_{O_2} and there were no perioperative respiratory complications. Only two patients complained of nausea and vomiting. Similarly, muscular hypertonia and shivering were not observed. We conclude that the combination of continuous propofol infusion and fentanyl was a successful anaesthetic technique in these young myotonic dystrophy patients undergoing peripheral surgery.

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Myotonic dystrophy, an autosomal dominant disorder, first described by Steinert in 1909, is the most common of the myotonic syndromes with a prevalence of three to five per 100 000.[1 2] Although a rare congenital form of the disease exists, in most patients the onset is between the second and fourth decades of life. Myotonic dystrophy is characterized by myotonia (incomplete muscle relaxation), marked wasting of the muscles of mastication, neck, pharynx and distal limbs, ptosis, frontal baldness, low intelligence and multisystem involvement. Extramuscular features include cataracts, cardiomyopathy, conduction abnormalities, restrictive lung disease, central and obstructive sleep apnoea syndrome, dysphagia, delayed gastric emptying and endocrine abnormalities such as hypothyroidism, primary hypogonadism, infertility and diabetes mellitus.[2]

Anaesthetic management of these patients is challenging and may pose a serious problem to the anaesthesiologist. Myotonia may be precipitated by hypothermia, shivering, and mechanical or electrical stimulation. Furthermore, sensitivity to sedative, anaesthetic and neuromuscular blocking agents may result in intraoperative and early postoperative cardiovascular and respiratory complications, as well as prolonged recovery from anaesthesia. We therefore performed a study to assess the adequacy of an anaesthetic regimen based on i.v. propofol in myotonic dystrophy patients undergoing oropharyngeal and neck surgery.

Patients and methods

Between 1993 and 1997, 13 patients with myotonic dystrophy scheduled for oropharyngeal and neck surgery were enrolled in an open prospective study. All patients complained of peripheral muscle weakness, which started at a median age of 6 yr (range 3–35) but were able to function adequately, with good physical mobility and without handicap. There was no history of systemic disease and none was taking medication. Physical examination showed wasting of thenar and masseteric muscles. Preoperative haematological and biochemical investigations, ECG, echocardiograpy and lung function tests were normal.

The study was approved by the Institutional Ethics Committee and consent was obtained from all patients or their parents. No pre-anaesthetic medication was adminis-

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tered. Prior to induction of anaesthesia, with the patient in the supine position, vital capacity and tidal volume were measured using an Ohmeda Modulus II anaesthetic machine pneumotachograph with a tight-fitting face mask. Intraoperative monitoring included electrocardiogram, non-invasive arterial pressure, pulse oximeter, capnograph, nerve stimulator and rectal temperature. The highest and lowest intraoperative arterial pressure and heart rate were documented. Anaesthesia was induced with fentanyl 0.05 mg, propofol 2.5 mg kg^{-1} and atracurium 0.5 mg kg^{-1}. After intubation of the trachea, the patients' lungs were ventilated with 70% N_2O in oxygen and anaesthesia was maintained with a continuous infusion of propofol 6 mg kg^{-1} h^{-1}, bolus fentanyl 2 μg kg^{-1} and incremental doses of atracurium 0.2 mg kg^{-1}. After patients had regained consciousness and four equal 'train of four' twitches were observed, the trachea was extubated. A 20% or greater decrease in systolic blood pressure was treated with i.v. ephedrine (5 mg).

Duration of anaesthesia (start of anaesthesia–extubation), recovery time (end of surgery–extubation), post-extubation tidal volume and vital capacity were recorded. Patients were admitted for 2–3 h to the post-anaesthetic care unit (PACU) prior to being discharged to the ward. On admission to PACU, ECG, NIBP, Sp_{O_2} as well as the occurrence of postoperative nausea and vomiting were recorded. Postoperative respiratory and cardiac complications and length of hospital admission were noted.

The mean highest and lowest intraoperative heart rate, systolic blood pressure, post-extubation tidal volume and vital capacity, and lowest postoperative Sp_{O_2} were compared to baseline values and analysed using the Mann–Whitney U-test. A P-value of <0.05 was considered significant.

Results

The following surgical procedures were performed: pharyngeal flap for correction of velopharyngeal incompetence (eight patients), pharyngeal flap and tonsillectomy (two patients), endoscopic surgery of the sinuses (FESS) for pansinusitis (one patient), cervical lymph node biopsy (one patient) and total thyroidectomy for papillary carcinoma of thyroid (one patient). The median age was 21 yr (range: 11–42 yr). The mean (SD) duration of anaesthesia was 104 (44) min, and the mean (SD) recovery time was 12 (11.5) min. The intraoperative highest and lowest systolic blood pressures were significantly different from the baseline (135 (14.5), 100 (18.7) versus 122 (8)) (P=0.01, P<0.001). On the other hand, only the lowest intraoperative heart rate differed significantly from the baseline (64.7 (14.2) versus 78.2 (13)) (P=0.01). Ephedrine was not required in any case. The mean postoperative Sp_{O_2} (97 (2.9)) did not differ from the preoperative (98 (1)) values. The median hospital admission was 2 days (range: 1–4 days).

There was no difference between mean preoperative and postoperative tidal volumes (334 (119) ml versus 330 (122) ml) (P=0.97). However, there was a significant decrease in mean postoperative vital capacity (965 (349) ml) from the preoperative value (1664 (566) ml) (P=0.0028). There were no perioperative respiratory or cardiac complications and bronchial secretions were not a problem. Only two patients complained of nausea and vomiting, but no treatment was required. Similarly, muscular hypertonia and shivering were not observed.

Discussion

Because of the marked sensitivity of myotonic dystrophy patients to sedative and anaesthetic agents and the increased risk of precipitating generalized myotonia by cold, shivering and drugs, the safest anaesthetic technique has still to be established. Dundee and thereafter Bourke initially used thiopental as an induction agent for myotonic dystrophy patients.[3 4] Both reported thiopental to induce prolonged apnoea and respiratory depression. However, later studies failed to confirm these reports.[6 7] In a recent retrospective study, 152 out of 219 myotonic dystrophy patients received thiopental without adverse effects.[5] These conflicting reports suggest that the prolonged apnoea attributed to thiopental may be due to an idiosyncratic peripheral effect and central nervous system depression commonly associated with the development of the disease.

Etomidate was used successfully in a myotonic dystrophy patient undergoing maxillo-facial surgery.[8] However, because etomidate has been shown to cause adrenal suppression, its use by continuous infusion is now questioned.[9]

The use of propofol as an induction and maintenance agent in myotonic dystrophy is controversial. Milligan was the first to report the uneventful use of propofol as an induction agent in myotonic dystrophy,[10] while White and Smyth administered a continuous infusion of propofol in a case undergoing prolonged oral surgery without mishap.[11] Speedy found that less than 1 mg kg^{-1} of propofol was sufficient to induce hypnosis and permit tracheal intubation.[12] However, when isoflurane was added to maintain anaesthesia, the patient developed severe intraoperative hypotension and prolonged postoperative unconsciousness and apnoea. Similarly, in a patient in whom a target-controlled propofol infusion system was used, recovery was prolonged for 1 h after the completion of surgery.[13] A generalized myotonic state was also reported after the i.v. administration of propofol.[14] As with thiopental, the cause of these variable exaggerated physiological responses to propofol can be associated with the severity of the disease.

Inhalation agents may be deleterious in patients suffering from myotonic dystrophy and should be used with caution. Deep inhalation anaesthesia may further risk the already compromised cardiovascular and respiratory systems of these patients, while postoperative shivering may precipitate myotonia. However, large concentrations of volatile anaesthetics have been shown to resolve myotonic contractions albeit at the expense of cardiorespiratory depression.[2]

Neuromuscular blocking drugs pose a particular problem in myotonic dystrophy. These patients are particularly sensitive to succinylcholine. Succinylcholine has an initial stimulating action on muscle.[15,16] This may result in the development of myotonia leading to difficulty in intubation and ventilation. Therefore, the use of succinylcholine is not recommended in myotonic dystrophy patients.[2,7,17]

In contrast, the non-depolarizing neuromuscular blocking drugs usually evoke a normal response. However, if muscle wasting exists, a prolonged response may occur necessitating the reversal of the muscle relaxant. The anticholinesterase drugs used for this purpose may also precipitate myotonia, presumably a result of increased sensitivity to the stimulatory effect of acetylcholine.[18,19] Although neostigmine has been found to be safe in some instances,[16,20] it would be prudent to rather use short-acting non-depolarizing muscle relaxants which do not require antagonism. In this context, atracurium, an intermediate-acting muscle relaxant, which is metabolized by Hoffman degradation may be the most suitable. Spontaneous recovery from atracurium has been shown to occur in under an hour.[17,21–23]

We found the combination of a continuous propofol infusion, fentanyl, atracurium and nitrous oxide in oxygen to be successful for patients undergoing oropharyngeal and neck surgery Exaggerated reactions to drugs and myotonia were not observed. The recovery period was smooth and relatively short (12 min), and only two patients had nausea and vomiting. There were no serious postoperative respiratory or cardiac complications.

Anaesthetic and surgical complication rates range between 8.2 and 42.9%.[5–7] The stable intraoperative period, uneventful recovery and lack of postoperative complications in our study may be explained by two factors. Firstly, our patients were young (median age 21 yr) and only had minor symptoms of the disease. Myotonic dystrophy is a slowly progressing multi-system disease with death occurring usually in the sixth decade of life.[17] Secondly, the surgical procedures in this study were peripheral. The prevalence of postoperative pulmonary complications has been reported to be as high as 38.1% after upper abdominal surgery in patients with myotonic dystrophy.[5] However, in none of these cases was propofol used as the main anaesthetic. In contrast, White and Smyth reported an uneventful perioperative period in a patient anaesthetized using a continuous infusion of propofol for abdominal hysterectomy.[11] Therefore, the effect of propofol-based anaesthesia on the surgical outcome in myotonic dystrophy patients undergoing major surgery needs further clarification.

In conclusion, the combination of propofol infusion, fentanyl, and atracurium with nitrous oxide in oxygen appears to be a suitable anaesthetic technique for young myotonic dystrophy patients undergoing peripheral surgery. Further studies are required to evaluate this anaesthetic technique in elderly patients suffering from myotonic dystrophy as well as those undergoing major surgery.

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Resistance of laryngeal mask airway and tracheal tube in mechanically ventilated patients

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We compared the airflow resistance of 7.5 and 8.5 mm internal diameter (i.d.) endotracheal tubes (ETTs) with that of a size 4 laryngeal mask airway (LMA[†]). We thought that any difference in the resistance of the devices alone might be offset by the resistance of the larynx. Sixteen adult ASA physical status I and II patients (14 males, two females) undergoing general anaesthesia were anaesthetized and paralysed with intravenous propofol, ketamine and vecuronium. After insertion of the LMA, controlled ventilation (tidal volume 10 ml kg^{-1}, frequency 12 min^{-1}) was established with three different settings for inspiratory flow (5.5, 7.5 and 12.5 ml kg^{-1} s^{-1}). Ventilation with the same settings was used after orotracheal intubation with an ETT of i.d. 7.5 mm (females) or 8.5 mm (males). The position of the LMA mask and the tip of the ETT were checked through a fibrescope. The resistance of the devices and, in case of the LMA, of the larynx, was derived by relating proximal and distal pressures (measured via catheters) to inspiratory flow. Four patients—young, tall men—had to be excluded from further study because of a leak around the LMA. In the remaining 10 males and two females, resistance of the LMA (mean (SD) at high flow, 1.19 (0.22) mbar·s $litre^{-1}$ in males) was less than that of the 8.5 mm i.d. ETT (3.34 (0.52) mbar·s $litre^{-1}$) ($P<0.01$). However, the structures between the LMA and the trachea added another, highly variable, resistance component, so that the mean resistance of the LMA and larynx together was similar (in males: 3.20 (2.71) mbar·s $litre^{-1}$) to that of the 8.5 mm ETT. In eight patients the epiglottis projected on to one-tenth to two-thirds of the distal opening of the LMA; this was in no case associated with greater resistance. Greater resistance occurred in two patients with a central LMA position and unobstructed view of the glottis and in one patient with marked lateral deviation. In conclusion, there is no clinically relevant difference between the resistance of a size 4 LMA plus that of the larynx and that of an 8.5 mm i.d. ETT.

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The laryngeal mask airway (LMA[†]) is popular as an airway during general anaesthesia. Unlike an endotracheal tube (ETT), it can be inserted into the pharynx without laryngoscopy and neuromuscular blockade and is the airway of choice for short procedures not requiring muscle paralysis; however, it is more frequently used for longer operations with controlled ventilation as well.

The LMA provides an adjunct which can be joined to the airway end-to-end, to avoid the reduction in diameter that happens when one tube (the ETT) is inserted into the lumen of another (the trachea).[1] Indeed, the tube part of a standard LMA is shorter and wider than a corresponding ETT. Bhatt and co-workers[2] found the resistance of an LMA was between one-sixth and half of that of a comparable ETT, depending on size and flow. They suggested that a patient breathing spontaneously would have to expend less work breathing on an LMA. This ignores the fact that the ETT ends in the trachea, i.e. beyond the glottis, while the LMA ends before the laryngeal entrance. The inspiratory resistance of the larynx should be added to that of the LMA for a true comparison.

We compared the inspiratory resistance of a standard ETT with that of a corresponding LMA plus the larynx. We hypothesized that any difference in resistance of the devices alone would be offset by the additional resistance of the larynx. Another aim of the study was to investigate how

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LMA position affected airflow resistance. Previous studies[3–9] have shown that deviations from a central position are common and that the epiglottis can project into a considerable proportion of the air passage in many patients. It has been suggested[8 10] that these variations in position are associated with increased airflow resistance, but no data have been presented to support or reject this assumption.

Materials and methods

Patient preparation and anaesthesia

After approval by the Hamburg board of physicians ethics committee, and with their written informed consent, 16 patients scheduled and regularly prepared for elective trauma, general or urological surgery were enrolled. Exclusion criteria were morbid obesity (weight >130% of norm), coagulation abnormalities, systemic disease, allergies, malformations or diseases of the head, neck, thorax or abdomen or the structures and organs within them.

The patients received oral midazolam (5.0–7.5 mg). For the study they were placed supine with the head resting on a 5 cm thick foam cushion. Anaesthesia was induced and maintained with propofol (2–3 mg kg^{-1} and infusion 6–12 mg kg^{-1} h^{-1}) and ketamine (1.0–1.5 mg kg^{-1} initially with repeated doses) after atropine 0.5–1.0 mg for reduction of secretions. Ketamine was used for analgesia in order to avoid the effects of opioids on chest wall mechanics.

Positioning of LMA and ETT

For the first part of the study, a size 4 LMA (Intavent (Cyprus) Ltd, Nicosia, Cyprus) was inserted by a standard technique, and its cuff was inflated with the recommended amount of air (30 ml). Absence of leaks was verified by ventilation with positive pressure. If leaks were detected by auscultation, the LMA was repositioned up to three times. The study was continued only if an apparently leak-free position was obtained. The position of the LMA relative to the structures of the larynx was inspected with a fibrebronchoscope (type BF P30, Olympus Optical Co. (Europe), Hamburg, Germany). Special attention was given to lateral deviation and to the proportion of the field of vision occupied by the epiglottis when looking from inside the distal opening. In all patients, the same experienced anaesthetist inserted the LMA and did the laryngoscopy.

A standard cuffed ETT (Mallinckrodt lopro, Mallinckrodt Medical, Hennef, Germany, internal diameter (i.d.) 7.5 mm for female patients, 8.5 mm for males) was used in the second part of the study, inserted through the mouth by conventional direct laryngoscopy. The position in the trachea was checked fibreoptically Because of the limited length of the pressure-measuring catheter (see below), the ETTs had to be shortened to 24 cm at the proximal end. Since the length of an airway has only minor impact on its resistance,[11] this shortening should not have influenced our results.

The devices were attached to the patient circuit of a standard anaesthesia machine (Cicero, Drägerwerk AG, Lübeck, Germany) via a 90° swivel bronchoscopy connector, a bacterium filter (type BB22-15M; Pall, Newquay, UK), and a combination of pneumotachygraph and proximal airway opening pressure (P_{ao}) tap (side stream spirometer; Datex Instrumentarium Corp., Helsinki, Finland).

Measuring equipment

A pressure-measuring catheter of 2.5 mm outer diameter, with closed tip and side holes (K-31; Baxter Healthcare Corporation, Deerfield, IL, USA) was placed through the LMA or ETT with the tip guided into the trachea under direct vision using a bronchoscope ('distal' catheter) An identical catheter was placed with its tip in the proximal end of the devices close to the swivel connector ('connector' catheter) and both were attached to individual transducers (Medex, Klein Winternheim, Germany) measuring pressure relative to atmosphere. The catheters were flushed with air frequently throughout the study; this reliably prevented plugging by mucus or condensation. Signals from these pressure transducers and from the sidestream spirometer (flow and P_{ao}) were displayed on a monitor (ASIII: Datex) and stored on a personal computer after digitizing at 100 Hz. The monitor was calibrated according to the manufacturer's specifications; standard pressures and a standard volume were recorded on the computer before each study for correction of the digitized signals. Earlier tests had shown that the ASIII monitor delays signal output by 50 ms (pressures) or 250 ms (signals from the sidestream spirometer). The tracks of the digital recordings were shifted appropriately, so the remaining phase shift between signals was <10 ms. Linearity and symmetry were verified for pressure measurements by appropriate reference pressures and for the flow measurement by applying the calibration volume (1 litre) in both directions with a wide range of flows.

Arterial pressure (cuff), heart rate (ECG), oxyhaemoglobin saturation (pulse oximeter) and end-tidal $P\text{CO}_2$ were monitored throughout the study (Marquette Electronics Inc., Milwaukee, WI, USA; Draegerwerk AG).

Experimental procedure

The patients were ventilated with 50% oxygen in nitrogen in intermittent positive pressure ventilation mode with 12 breaths min^{-1}, a tidal volume of 10 ml kg^{-1} and an inspiratory:expiratory time (I:E) ratio of 1:1.5 To obtain measurements at different inspiratory flow rates while keeping tidal volume and I:E ratio constant, the relation between the inspiratory flow phase and end inspiratory pause was varied: Each measurement block consisted of three sets of 10–30 breaths each with an end inspiratory pause of 0%, 30% and 60% of inspiratory time, respectively, resulting in flows of 5.5, 7.5 and 12.5 ml kg^{-1} s^{-1}, respectively. With each device, one block of measurements was made with the 'distal' catheter located in the trachea and one after retraction of this catheter to the 'connector' position. By comparing the data from the two blocks, the effect of the catheter on the devices' resistance could be estimated. In eight patients, another block of measurements was made with the tip of the 'distal' catheter located in the distal opening of the LMA, so in these patients the resistance of the LMA could be distinguished from that of the larynx.

To avoid unnecessary manipulation in the patients' upper airway, the LMA was studied first in all patients. The ETT was then placed and left there for the rest of the anaesthesia. Since the variables measured were bound to be independent of time, we did not expect the order to have any effect. As endotracheal intubation was facilitated routinely by neuromuscular blockade, both devices were studied after administration of vecuronium (0.1 mg kg^{-1} initially, repeat doses of 0.05 mg kg^{-1} after 30 min) to allow comparability. In five patients additional measurements were made with the LMA before giving the relaxant, to provide data on the effects of neuromuscular blockade.

Data analysis

The recorded signals were supplemented with a trace for the drop in resistive pressure along the devices and the larynx. This was obtained by digitally subtracting the pressure measured with the 'distal' catheter from that at the 'connector' catheter. The flow signal was digitally integrated for calculation of tidal volume. Flow during the last 500 ms of inspiration was used as the denominator in resistance calculations. All respiratory mechanics results were means from the last six breaths of each setting.

Resistance values were calculated primarily by dividing the drop in resistive pressure between the connector and the trachea (and between the connector and tip of the LMA in eight patients) by the simultaneously measured flow values. However, this resistance was, inevitably, increased artificially by the 'distal' catheter passing through the devices and the larynx. The data were corrected for this artefact by a second method for resistance calculation: When inspiratory flow stops, pressures throughout the respiratory system decrease suddenly, because the resistive loads distal to any point of measurement no longer have to be addressed by a driving pressure component. If an end inspiratory pause follows the cessation of flow, as in our study in the setting with medium and high flows, the difference between the peak pressure immediately preceding the cessation and the value directly after it (ΔP_1) can be divided by the flow before cessation, yielding resistance of all structures distal to the point of measurements [12]. In this study the ΔP_1 method was applied to P_{ao}; comparison of the values with the 'distal' catheter in the trachea or at the tip of the LMA, respectively, to those after retraction to the 'connector' position allowed quantification of the increased resistance caused by the catheter passing through the structures of interest when in the 'distal' position. The catheter-derived resistances were corrected for this artefact. Since the artefact could only be quantified at medium and high flows (see above), corrected resistance values are available only for those settings. Since the ΔP_1 method is prone to noise, the artefact correction introduced a certain amount of scatter, but this did not influence the main findings of the study.

Theoretically, simple differences between the resistances of the devices could have been measured entirely based on the ΔP_1 method, obviating the need for catheter measurements. This simplification, however, would have generated several problems: (i) no absolute values of resistance would have been available, making comparison with published data difficult; (ii) intubation-related changes in resistance of structures distal to the trachea, i.e. bronchi, lung parenchyma and chest wall, could not have been distinguished from changes of the values under study, thus introducing a substantial source of error; (iii) separate consideration of LMA and larynx would not have been possible.

Data are reported as means (SD) unless stated otherwise. Since comparison of devices always included ETTs, only the data for the male patients were tested by Wilcoxon's ranked sign test; differences were considered significant if P was <0.05 (SYSTAT version 5.1 under MacOS). There were too few female patients for statistical testing to be valid for data from these patients.

Results

Data from 12 of the patients were available for analysis. In two patients, audible leaks around the LMA persisted despite careful repositioning, so study of these patients was cancelled before any data acquisition; in another two, analysis of inspiratory and expiratory tidal volume indicated a leak of >100 ml $breath^{-1}$ when lungs were ventilated through the LMA, so data from these patients were excluded from further analysis. All patients excluded were young, tall men. Table 1 summarizes the patient characteristics.

Figure 1 shows the inspiratory resistance of LMA alone (left panel), LMA plus larynx (middle) and ETT (right) as a function of flow before correction for the artificial increase in resistance by the 'distal' catheter in place. Plots spanning corresponding flow values in the three panels refer to the same patient, as flow was determined by tidal volume and thus by body weight. Low flow was on average 0.45 litres s^{-1}, medium flow 0.63 litres s^{-1} and high flow 1.05 litres s^{-1}. Three main observations can be made: (i) the resistance of the LMA alone and of the ETT had a nearly linear flow–resistance relationship; scatter was negligible; (ii) the resistance of the LMA alone was smallest, while that of the 7.5 mm i.d. ETT used for the two females was greatest; (iii) anatomical structures distal to the LMA showed a highly variable additional resistance.

Figure 2 shows the corresponding resistance after correction for the catheter artefact. Since the correction was based on the ΔP_1 method and required an end inspiratory pause, only values from medium and high flows were available. The data, taken in conjunction with those from the corresponding panels of Figure 1, allow several conclusions: (i) the correction slightly increased the scatter; (ii) as expected, the additional resistance caused by the measuring catheter is lowest in the device with the widest lumen, i.e. the LMA (0.33 (0.29) mbar·s litre^{-1} at high flow), and increases with narrowing of the lumen (8.5 mm i.d. ETT, 1.74 (0.32) mbar·s litre^{-1}; 7.5 mm i.d., 4.31 (0.05) mbar·s litre^{-1}); (iii) the resistance of the structures between the LMA and the trachea was nearly as high and variable as before correction.

In Figure 3, the corrected resistance data are presented in a different way to improve the presentation of group mean data. Standard deviations are only shown for males. The resistance of the devices alone corresponded to that found by other authors:[2 11 13 18] that of the LMA (1.19 (0.22) mbar·s litre^{-1} in males and 1.98 (0.44) mbar·s litre^{-1} in females, at high flow) was smaller than that of the ETT (3.34 (0.52) mbar·s litre^{-1} for 8.5 mm i.d ($P<0.01$ versus LMA) and 6.39 (2.50) mbar·s litre^{-1} for 7.5 mm i.d). The resistance of LMA plus larynx, however (3.20 (2.71) mbar·s litre^{-1} in males, 6.14 (4.27) mbar·s litre^{-1} in females) was similar to that of the ETT ($P>0.1$; only males compared). As in the other figures, the scatter of resistance was largest for LMA plus larynx, suggesting high variability in the resistance of the structures distal to the LMA. One each of the male and female patients showed excessively high resistance of the larynx; because fewer females were

Table 1 Patient characteristics

Patient	Gender	Age (yr)	Weight (kg)
1	male	52	75
2	female	35	90
3	male	50	82
4	male	67	95
5	male	43	74
6	female	52	67
7	male	59	72
8	male	27	70
9	male	65	63
10	male	58	73
11	male	56	64
12	male	64	82
Median		54 00	73.50
Range		27–67	63–95

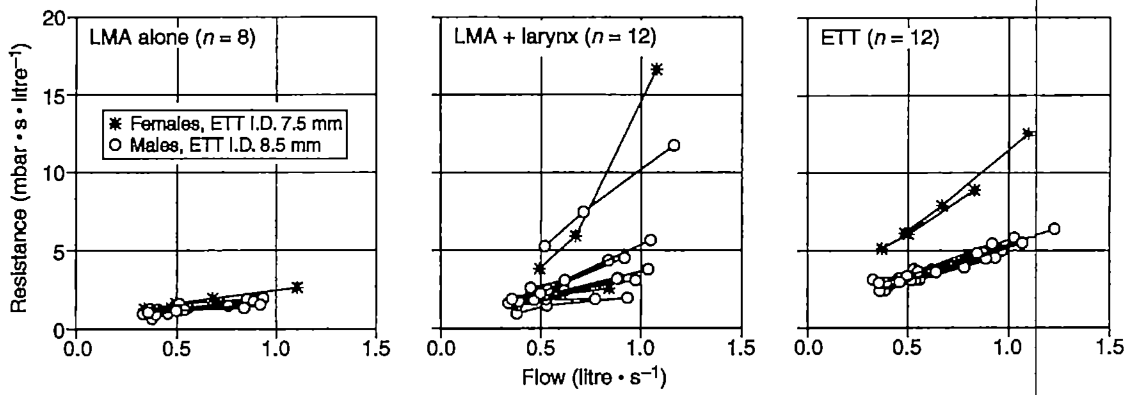

Fig 1 Resistance of devices before correction for artefact by measurement of catheter.

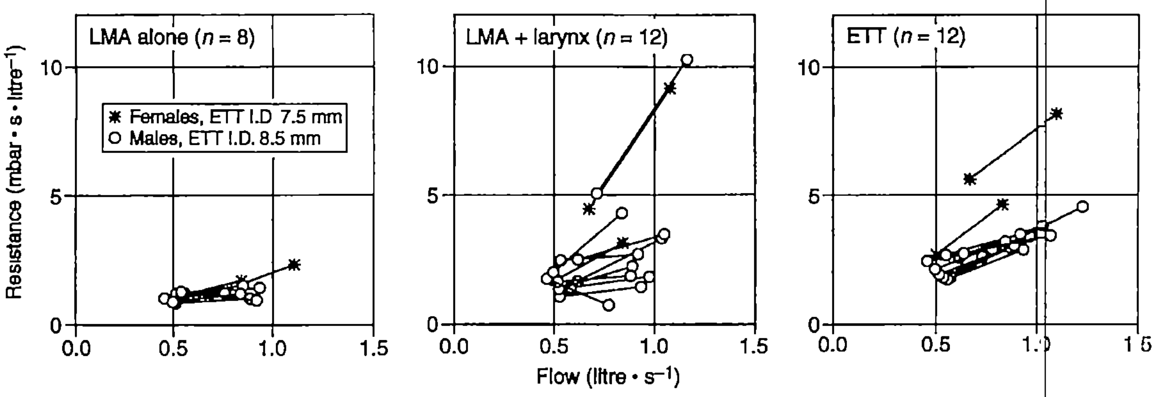

Fig 2 Resistance of devices after correction for artefact by measurement of catheter.

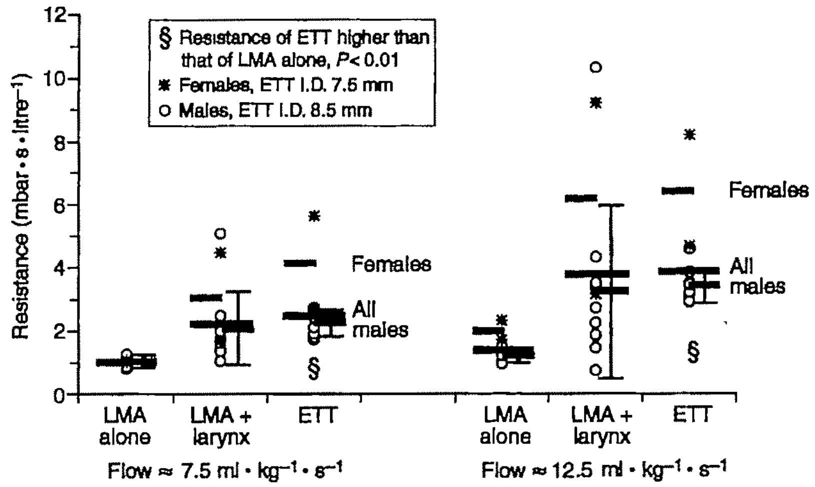

Fig 3 Summary of corrected resistance at medium and high flow. The figure shows individual data and mean values for males and females separately and for the whole group. Standard deviations are indicated for males only.

Table 2 Endoscopy 'Distal opening' is the proportion of the field of vision occupied by the epiglottis (E) or anterior wall of the trachea (AW). Patients 2 and 4 made a whooping sound during inspiration through LMA

			LMA			
Patient	**ETT endoscopy**		**Leakage (ml per ml of tidal volume)**	**Endoscopy**		**Resistance including larynx (mbar s^{-1} litre^{-1})**
	Deviation	**Distal opening**		**Deviation**	**Distal opening of endoscope**	
1	–	–	0	left	1/10 (E)	1.80
2	–	–	0	–	0	9.16
3	–	–	0	right	2/3 (E)	3.30
4	–	–	30/970	–	0	10.30
5	left	–	0	left	0	1.41
6	–	–	60/690	–	1/4 (E)	3.12
7	–	–	0	–	1/4 (E)	2.21
8	–	1/3 (AW)	0	–	1/2 (E)	1.84
9	–	–	0	dorsal	0	0.70
10	–	–	0	–	4/10 (E)	2.67
11	–	–	0	right (marked)	1/2 (E)	4.29
12	–	–	0	–	1/2 (E)	3.45

studied, the impact on the mean value was much larger in the female subgroup. In the other female patient the resistance of the larynx was in the same range as that of a male larynx.

The data for the LMA alone and the 8.5 mm i.d. ETT were fitted to a common second-order polynomial equation, Rohrer's equation, relating the pressure drop, ΔP, along a tube to the flow through it:

$$\Delta P = (K_1 \times \text{flow}) + (K_2 \times \text{flow}^2)$$

In this study, K_1 and K_2 for the LMA were 0.08 and 1.54 respectively (so ΔP was 1.62 mbar at a flow rate of 1 litre s^{-1}), while those for the ETT were 0.32 and 3.21, respectively (so ΔP was 3.53 mbar at a flow rate of 1 litre s^{-1}). This underscores the similarity between the resistance found in the present study and those reported previously.[2 11]

Confidence intervals for resistance values are not reported, because the variability caused by individual differences in flow rate would have to be eliminated first by deriving a resistance value at a normalized flow. For the devices alone this can be done by fitting the data as described in the paragraph above. However, the absence of such a clear relationship for the most interesting data, namely those from the LMA plus larynx, precludes such procedure in this context.

Table 2 summarizes endoscopic findings and other observations. Resistance data for the LMA plus larynx are included as reference. Two patients made a whooping noise during inspiration when ventilated through the LMA, and one showed a marked lateral deviation of the LMA; these were the three patients with especially high resistance of LMA plus larynx. In eight patients the epiglottis covered between one-tenth and two-thirds of the distal opening of the LMA, but this was not associated with increased resistance. In the two patients with a whoop and high resistance, the epiglottis could not be seen; the entire glottis could be seen from the distal opening of the LMA.

Discussion

We found that there was less airflow resistance with a size 4 LMA than with a corresponding ETT. The anatomical structures between the LMA and the trachea imposed an additional highly variable resistance, so overall resistive pressure drops between the airway opening and the trachea were of the same magnitude.

The resistance of artificial airways is of interest because a spontaneously breathing patient has to work to overcome it. Previous *in vitro* studies[2,13] found that the resistance and the additional work of breathing caused by standard LMAs are approximately one-sixth to half of those elicited by comparable ETTs (the range reflects the fact that there is a range of ETT sizes corresponding to a single LMA size). This difference is not surprising considering the larger diameter of the LMA tube: the work of breathing is inversely related to the third to fourth power of the tube diameter,[14] depending on breathing pattern, while length only makes a minor difference.[11] The recently introduced reinforced LMAs have narrower tubes, so their resistance is greater than that of standard LMAs and similar to that of ETTs.[13] However, an ETT bridges the larynx and thus eliminates its resistance. Thus, work while breathing through an ETT has been found to be equivalent to that during breathing through a standard LMA, and even less than that during breathing through a reinforced LMA with its narrower tube.[13] We found that the anatomical structures between the LMA and trachea had a sizeable and highly variable resistance of their own. On average, this resistance (the difference between the resistance determined for the LMA alone and that of the LMA plus larynx) amounted to 2.3 mbar·s litre^{-1} at high flow and reduced the differences between LMA and ETT resistance to insignificant and clinically irrelevant amounts. These results support those of Ferguson and colleagues,[15] who studied spontaneously breathing awake volunteers. They found that the resistance of the airways including an LMA was similar to that found for airways including an ETT by Gal and Suratt.[16] Normal upper airway resistance is between 0.5 and 1.0 mbar·s litre^{-1} during quiet breathing,[17] i.e. at flows comparable to the medium or low flows in our study. In contrast, Boisson-Bertrand and co-workers[18] found that the upper airways did not contribute to the overall resistance of the respiratory system resistance during mechanical ventilation via an LMA. The discrepancy might be result from the fact that upper airway resistance was not measured directly in that study.

Because of the small number of patients, the present study might not show a true difference between the resistance of the ETT and that of an LMA plus larynx. However, because of the high variability of laryngeal resistance, many patients would have to be studied to find a difference, which cannot be expected to be of a clinically relevant magnitude.

The relevance of the additional work of breathing imposed by airways can also be questioned in general. This work component is of the same order of magnitude as that naturally imposed by the respiratory system, and healthy adults should be able to easily overcome it with the force reserve of their respiratory muscles

However, the resistance of the structures between a LMA and the trachea is clinically relevant from a different point of view: major complications known to be associated with the use of the LMA,[19] i.e. laryngospasm and bronchospasm, likewise increase resistance, often immediately after LMA insertion. The anaesthetist has to distinguish these complications from an increase in resistance for mechanical reasons. The latter requires a different therapy if any (namely repositioning of the device), which is not indicated in the case of laryngospasm or bronchospasm.[19,20] It might be reasonable to increase the depth of anaesthesia at first, perform auscultation for differential diagnosis, and then attempt to reposition the device.

The study also aimed to discover the degree to which highly variable resistance of the larynx and the surrounding structures might be related to individual differences in the interactions of the LMA with the upper airway. The position of the epiglottis relative to the LMA has been of concern for several authors. Studies using magnetic resonance imaging, conventional radiography and/or fibreoptic endoscopy showed that, in 35–65% of patients, the epiglottis comes to lie within the cuff of the LMA and in most of these is folded down.[3,5–9] The epiglottis might occupy up to 100% of the field of view when looking down on the distal opening of the LMA with a fibrescope. This has been postulated to be a potential reason for obstruction,[8,10] but a correlation has not been found. As Brain points out,[20] the endoscopic view is two-dimensional, so the fact that the epiglottis can be seen—even in large parts of the field of view—does not preclude air from passing around it. Our study supports the notion that visibility of the epiglottis is not associated with a marked increase in resistance. Indeed, in the two patients in whom resistance was greatest, the view of the glottis was completely unobstructed. As the visibility of the epiglottis was not associated with increased resistance, no attempts were made to quantify the area of visual obstruction more precisely or to correct for the geometry of the fibrescope.

Nandi and co-workers[7] point to an important potential mechanism for obstruction. They found that the typical anterior displacement of the cricoid cartilage by the blocked LMA might render the vocal cords short, slack and partially adducted. In our study, both patients with high resistance were ventilated with relatively high tidal volumes (and, thus, inspiratory flows) because of their high body weight. The whooping sound associated with inspiration in these, and only these, patients gave rise to the suspicion that the inspiratory flow itself caused a narrowing of the glottis by a Bernoulli-like effect of flow limitation in an elastic tube. We also noted that, in one patient, the overall resistance diminished when the measuring catheter was retracted from the glottis. This resembled findings by Pedersen and Ingram,[21] who showed that a foreign body introduced into an elastic tube can promote collapse and aggravate flow limitation.

Righini and colleagues[22] found that the inspiratory resistance shown by a size 3 LMA while *in situ* in five patients was almost twice that measured *in vitro*. These authors speculated that this was caused by a narrowing of the distal LMA opening brought about by blocking the LMA cuff within the hypopharynx. However, the distal pressure was measured with a catheter extending 15 mm beyond the distal opening. Our endoscopic findings suggest that, in this position, Righini and co-workers were already measuring a considerable part of the resistance posed by the anatomical structures, so that conformational changes of the LMA outlet might not have had the impact ascribed to it by these authors.

In conclusion, we found no statistically significant or clinically relevant difference between the resistance of a size 4 LMA plus that of the larynx and that of an 8.5 mm i.d. ETT. The resistance of the anatomical structures between the LMA and the trachea is sizeable and highly variable. These findings extend and complement previous *in vitro* studies. In addition, they suggest that an LMA might change upper airway geometry in a way that promotes elevation of resistance.

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Influence of different colloids on molecular markers of haemostasis and platelet function in patients undergoing major abdominal surgery

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Synthetic colloids have been reported to cause haemorrhagic complications. The effects of perioperative volume replacement with 4% gelatin (n=20), 6% low-molecular weight (LMW) hydroxyethyl starch (HES) (Mw: 70 000 dalton; HES 70/0.5; n=20) and 6% medium-molecular weight (MMW) HES (Mw: 200 000 dalton; HES 200/0.5; n=20) on haemostasis were assessed in patients undergoing major abdominal surgery. Volume was administered to keep central venous pressure (CVP) between 10 and 14 mm Hg. Conventional global coagulation tests, molecular markers of coagulation, and platelet function (using a platelet function analyser (PFA-100™) with ADP as inductor) were monitored prior to surgery (T0), at the end of surgery (T1), 4 h after the end of surgery (T2), and on the morning of the first postoperative day (T3). Significantly more gelatin (2900 (SD 320) ml) than HES 200 (2150 (312) ml) was given during the study period. Bleeding and the use of allogeneic blood–blood products were similar in all groups. Markers of thrombin generation (F1+2), of thrombin neutralization (TAT III complex), and of fibrin formation and its degradation (D-dimer) increased significantly during and after surgery without showing significant group differences. Factor VIII and von Willebrand factor (vWF) also increased in all groups beyond the normal range, showing the significantly highest increase in the gelatin-treated group (VIII: from 173 (36) to 266 (33) U dl^{-1}; vWF: from 164(33) to 238 (31) U dl^{-1}). Platelet function remained within the normal range and without group differences throughout the study period. We can conclude that all three solutions can be used safely in patients undergoing major abdominal surgery with regard to the haemostatic process.

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During surgery, absolute or relative blood volume deficits often occur either due to bleeding (absolute hypovolaemia) or vasodilation mediated by various vasodilating substances (relative hypovolaemia). The most important objective of volume therapy in this situation is to maintain a stable haemodynamic state and tissue perfusion without inducing side effects. The inherent risk of transmission of viral and immunological diseases has forced us to reduce the use of allogeneic blood. A variety of synthetic colloidal solutions have been introduced to enhance blood volume. The ideal regimen of volume replacement has been the focus of debate for several years. In spite of the widespread use of synthetic colloids in several countries, there is still considerable concern that synthetic colloids may have adverse effects on coagulation.[1–3] Some studies suggest that colloids [e.g. gelatin or hydroxyethyl starch (HES)] are effective and safe substitutes for blood loss without relevant adverse effects on coagulation.[4 5] Others showed increased bleeding tendency with colloids and suggested that they should be avoided especially in patients at risk of increased bleeding.[6] Most of these studies, however, have assessed only conventional coagulation data. Serial monitoring of molecular markers of haemostasis is more helpful for the diagnosis of coagulation disorders.[7] The present study was designed to evaluate the influence of intraoperative volume replacement with three different colloids in patients undergoing major abdominal surgery on the following markers of haemostasis: prothrombin fragment F1 + 2 (as a marker of thrombin generation); TAT III (as a marker of thrombin neutralization); D-dimer (as a marker of fibrin formation and its

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degradation); and the factor VIII–von Willebrand factor (vWF) system (as a marker of endothelial injury). Additionally, platelet function was assessed using the PFA-100™ system in which coagulation is simulated close to normal conditions.[8 9]

Methods

The study was approved by the Ethics Committee of the hospital and all patients gave written informed consent. Sixty consecutive patients undergoing major abdominal surgery were included in the study. Exclusion criteria were cardiac insufficiency (NYHA class III–IV), renal insufficiency (serum creatinine >2 mg dl^{-1}), liver dysfunction (aspartate aminotransferase >40 U l^{-1}, alanine aminotransferase >40 U l^{-1}), preoperative anaemia (haemoglobin (hgb) <10.0 g dl^{-1}), preoperative coagulation abnormalities (platelet count <100 nl^{-1}; activated partial thromboplastin time (aPTT) >70 s; fibrinogen <2 g dl^{-1}; anti-thrombin III <40%), non-steroidal therapy or use of cyclooxygenase inhibitors. Standard anti-thrombotic prophylaxis using low-molecular weight heparin administered s.c. the evening before surgery was used in all patients.

According to preoperative randomization (using blinded envelopes), the patients were prospectively separated into three groups (each group *n*=20). Patients received either 4% modified gelatin solution (Gelafundin (B. Braun, Melsungen, Germany)), a low-molecular weight (LMW) HES solution (mean molecular weight (Mw) 70 000 dalton, degree of substitution (DS) 0.5; 6% HES 70/0.5 (Rheohes, B. Braun)), or a medium-molecular weight (MMW) HES (Mw 200 000 dalton, DS 0.5; 6% HES 200/0.5 (Hemohes, B. Braun)). Volume was given to maintain central venous pressure (CVP) between 10 and 14 mm Hg. Packed red blood cells (PRBC) were administered when the haemoglobin was <9 g dl^{-1}. Fresh frozen plasma (FFP) was given only to maintain haemostasis (when aPTT >70 s, fibrinogen <2 g dl^{-1}, antithrombin III <40%, and bleeding occurs). Platelets were infused when the platelet count was $<30\times10^9$ $litre^{-1}$. Ringer's lactate was given to compensate fluid loss by sweating, gastric tubes and urine output, or as a solvent for drugs (e.g. antibiotics). Ringer's lactate 500 ml h^{-1} was administered routinely in all patients during surgery.

The patients were premedicated with lorazepam 2.0 mg. Anaesthesia was induced in all groups with fentanyl 3 µg kg^{-1}, thiopental 5 mg kg^{-1} and atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained by titrating sufentanil, atracurium and isoflurane as indicated clinically. The lungs of all patients were mechanically ventilated with 60% N_2O in oxygen to keep the Sa_{O_2} >95% (continuous oximetry) and the end-expiratory CO_2 between 35 and 40 mm Hg (continuous capnography). To maintain normothermia during surgery, a rewarming system (Warmtouch™) and fluid warmers were used. After surgery, the patients were transferred either to an intensive care unit (ICU) or to an intermediate care unit. Perioperative monitoring included continuous arterial pressure measurement (radial artery), ECG, pulse oximetry, CVP, body temperature (oesophageal), urine output and arterial blood–gas analysis. The anaesthetists who were responsible for the patients' management were not involved in the study and blinded to the grouping.

Coagulation measurements

From central venous blood samples, standard coagulation data (antithrombin III (AT III), fibrinogen, platelet count, activated partial thromboplastin time (aPTT)) were measured using routine laboratory tests. D-dimer (turbidimetric method, Roche Diagnostics, Mannheim, Germany, interassay coefficient of variability in normal ranges (CV): <10%), F1+2 (ELISA, Dade/Behring, Marburg, Mannheim, CV: 6–13%), thrombin/anti-thrombin III (TAT; ELISA, Dade/Behring, Marburg, CV: 6–9%), factor VIII activity (one-stage clotting assay; Roche Diagnostics, Mannheim, Germany, CV: 7%), von Willebrand factor (vWF; turbidimetric method, Roche Diagnostics, Mannheim, Germany, CV: <10%), collagen-binding activity of von Willebrand factor (vWF: CBA; sandwich ELISA, Immuno-Diagnostika, Heidelberg, Germany, CV: 17%) were also measured from the blood samples. Platelet function was measured using a Platelet Function Analyser PFA-100™ system (Dade/Behring, Marburg, Germany). The time required for the platelet plug to occlude the aperture is called the 'closure time' and is indicative of platelet function.[8] When the PFA-100™ data using ADP as an inductor are abnormal, it is likely that patients have a platelet defect that impairs primary haemostasis.[9] The normal range for PFA-100™ system using ADP as an inductor has been determined to be 77–130 s.[9] Results from all coagulation data represent the mean from duplicate measurements. Blood sampling was performed at T0 (prior to surgery), T1 (end of surgery), T2 (4 h after surgery) and T3 (first postoperative day).

Statistics

SPSS/PC+ software (V4.0 SPSS, Chicago, USA) was used for statistical analysis. All measured and calculated data were normally distributed (tested by the Kolmogorov–Smirnov test) and all data are presented as mean (SD). Perioperative data were analysed using the Student's *t*-test, Fisher's exact test, or Wilcoxon rank sum test as appropriate. A two-way analysis of variance for repeated measurements (ANOVA, followed by Scheffe's test) was used to determine the effects of group, time and group–time interactions for each measured coagulation variable. In the presence of significant time differences, pair-wise comparisons against baseline values were evaluated using multiple paired *t*-tests. *P*-values <0.05 were considered significant.

Table 1 Patient's characteristics and perioperative data Mean (SD); ICU, intensive care unit; PRBC, packed red blood cells, FFP, fresh frozen plasma

	Gelatin (*n*=20)	**HES 70/0.5 (*n*=20)**	**HES 200/0.5 (*n*=20)**
Age (yr)	62 (11)	63 (10)	63 (12)
(Range)	44–80	40–76	43–77
Sex (F/M)	8/12	8/12	10/10
Height (cm)	167 (8)	169 (8)	168 (7)
Weight (kg)	72 (13)	77 (13)	72 (17)
ASA (II/III)	9/11	10/10	8/12
Duration of (min)			
Surgery	198 (76)	191 (59)	190 (62)
Anaesthesia	253 (85)	256 (64)	248 (100)
Type of surgery			
Rectum resection	9	8	9
Gastrectomy	3	4	3
Whipple operation	4	3	2
Oesophageal surgery	1	2	2
Pancreas resection	3	3	4
Allogeneic blood–blood products (units group^{-1})			
PRBC	29	25	26
FFP	7	8	6
ICU/intermediate care			
(No of patients)	16/4	15/5	15/5
Survivors	19	19	20

Table 2 Infused volume (cumulative), haemodynamics and temperature Mean (SD), MAP, mean arterial blood pressure, CVP, central venous pressure, POD, postoperative day #$P<0.05$ different to the HES 200/0.5 group

	Baseline	**After surgery**	**Four hours after surgery**	**First POD**
Crystalloids (ml)				
Gelatin	870 (250)	2380 (860)	2710 (1050)	5150 (1090)
HES 70/0.5	960 (280)	2250 (810)	2830 (1050)	5200 (1080)
HES 200/0.5	820 (200)	2110 (820)	2630 (1190)	5480 (1040)
Colloids (ml)				
Gelatin		2250 (460)	2530 (400)	2900 (320)#
HES 70/0.5		1910 (310)	2180 (350)	2360 (410)
HES 200/0.5		1880 (310)	1950 (410)	2150 (312)
Blood loss (ml)				
Gelatin		960 (310)	1200 (330)	1310 (380)
HES 70/0.5		990 (230)	1290 (360)	1350 (390)
HES 200/0.5		910 (300)	1100 (300)	1250 (340)
MAP (mm Hg)				
Gelatin	92 (17)	92 (18)	86 (11)	87 (12)
HES 70/0.5	81 (8)	85 (10)	86 (13)	88 (11)
HES 200/0.5	79 (12)	91 (15)	88 (13)	81 (9)
CVP (mm Hg)				
Gelatin	9.1 (3.5)	12.2 (2.7)	12.6 (3.1)	12.3 (2.5)
HES 70/0.5	9.4 (3.4)	12.3 (1.7)	11.4 (3.1)	11.8 (2.1)
HES 200/0.5	8.9 (2.2)	11.9 (2.1)	12.6 (2.6)	11.1 (2.8)
Temperature (°C)				
Gelatin	35.7 (0.5)	34.4 (0.7)	35.5 (0.7)	36.2 (0.7)
HES 70/0.5	35.6 (0.4)	34.4 (0.5)	35.5 (0.4)	36.1 (0.5)
HES 200/0.5	35.7 (0.6)	34.5 (0.8)	35.9 (0.5)	36.3 (0.4)

Results

Patient characteristics and data from the perioperative period are presented in Table 1. The use of PRBC and FFP was similar in all groups (Table 1). Haemodynamic variables and oesophageal temperature did not differ between the groups (Table 2). Similar volumes of crystalloid solutions were infused perioperatively (Table 2), but significantly more gelatin than HES 200/0.5 was needed to keep the CVP between 10 and 14 mm Hg (Table 2). Blood loss was comparable at each data point for all groups (Table 2). The degree of haemodilution (haemoglobin) was comparable among the groups throughout the study period (Table 3). Standard coagulation data (platelet count, aPPT, fibrinogen, AT III) did not show significant group differences within the study period (Table 3).

F1+2 increased significantly from baseline values in all patients (Fig. 1). At the end of the study, F1+2 plasma levels

Table 3 Standard laboratory data Mean (SD), POD, postoperative day $^*P<0.05$ different to baseline

	Baseline	After surgery	Four hours after surgery	First POD
Haemoglobin (g dl^{-1})				
Gelatin	12.4 (1.5)	9.7 (1.2)*	10.9 (1.1)*	10.6 (1.3)*
HES 70/0.5	12.6 (1.3)	10.1 (1.3)*	10.7 (0.9)*	10.3 (1.2)*
HES 200/0.5	12.2 (1.8)	10.2 (1.1)*	10.6 (1.0)*	10.5 (1.3)*
Platelet count (nl^{-1})				
Gelatin	264 (64)	206 (75)*	219 (81)*	236 (74)
HES 70/0.5	271 (92)	192 (89)*	213 (82)*	239 (84)
HES 200/0.5	260 (88)	211 (78)*	208 (72)*	230 (87)
aPTT (normal: 25–40 s)				
Gelatin	34.4 (3.9)	37.6 (3.9)	39.4 (4.4)	42.1 (4.0)
HES 70/0.5	35.1 (3.5)	38.3 (3.8)	38.7 (4.7)	39.9 (4.9)
HES 200/0.5	35.9 (4.9)	40.1 (4.3)	43.7 (3.3)	41.9 (4.5)
Fibrinogen (normal: 150–400 mg dl^{-1})				
Gelatin	390 (51)	254 (39)*	299 (44)*	438 (48)
HES 70/0.5	376 (61)	234 (52)*	279 (61)*	416 (42)
HES 200/0.5	370 (55)	256 (47)*	282 (67)*	412 (44)
AT III (normal: 80–100%)				
Gelatin	85 (14)	57 (9)*	70 (11)*	75 (9)
HES 70/0.5	83 (9)	55 (8)*	65 (11)*	78 (11)
HES 200/0.5	84 (11)	59 (10)*	62 (9)*	77 (12)

had almost returned to baseline. Starting from normal concentrations at baseline (<1 mg l^{-1}), D-dimer levels increased significantly without showing group differences (Fig. 1). TAT complex was also almost normal at baseline (<4 μg l^{-1}), increased significantly beyond normal levels in all three groups, and was still elevated beyond normal at the end of the study in all patients (Fig. 1). Factor VIII activity and vWF were similar at baseline in all groups (Fig. 2). In the gelatin-treated patients, factor VIII (from 173 (36) to 266 (33) U dl^{-1}) and vWF (from 164 (33) to 238 (31) U dl^{-1}) increased significantly more than in the HES 70- and HES 200-treated groups (Fig. 2). On the morning of the first postoperative day, both factor VIII and vWF were significantly higher than at baseline in all groups, but there were no differences between groups. vWF : CBA increased similarly (P=0.07) in all three groups (Fig. 2). The platelet function test using ADP as an inductor remained within the normal range and without differences between the groups throughout the study period (Fig. 3).

Discussion

The major result of the present study was that, despite infusing more than 2500 ml of each colloid, blood loss, use of allogeneic blood–blood products and coagulation markers did not differ between the groups. While no differences in blood loss were found in the present study, a higher blood loss in HES- (6% HES 200/0.5) than in gelatin-treated patients undergoing primary total hip replacement has been reported.[11] Other reports have used first generation, high-molecular weight (HMW), highly substituted HES (6% HES 450/0.7 (e.g. hetastarch)).[1 6] In healthy volunteers, a decrease in factor VIII and a prolongation of aPTT were noticed after 1000 ml of HMW-HES.[12] Patients in whom large amounts of HMW-HES (>1000 ml) were used had a decrease in factor VIII : C and vWF : AG.[13] After infusion of 1500 ml of HMW-HES in surgical patients, Conroy *et al.*[14] showed a significant decrease of factor VIII : C levels (69% of baseline). Although HES with lower MW and lower DS seems to cause fewer effects on the factor VIII system,[2 15 16] negative effects of LMW- and MMW-HES on haemostasis have also been shown. In healthy volunteers, Kapiotis *et al.*[17] demonstrated a specific lowering effect on factor VIII : C concentrations after 500 ml of MMW-HES (200 000 dalton; DS 0.5). They also found no specific influence on systemic activation of blood coagulation (measured by TAT plasma levels) and the fibrinolytic system (e.g. D-dimer).

Some *in vitro* studies have described advantages of gelatin compared to HES with regard to coagulation.[18–20] However, in healthy volunteers, 1000 ml of gelatin (Gelofusin) resulted in a significant decrease in vWF (–32%) most likely due to a binding of vWF to gelatin at its binding sites.[21] Additionally, TAT (–45%) and F1+2 (–40%) decreased significantly more than could be expected by haemodilution, indicating that gelatin in healthy volunteers resulted in a significant impairment of primary haemostasis and thrombin generation.[21] The defect in primary haemostasis appears to be related to a gelatin-induced reduction in von Willebrand factor. In an *in vitro* study, Tabuchi *et al.*[22] found that gelatin reduced the velocity and the extent of ristocetin-induced platelet aggregation, whereas aggregation by ADP was not affected. They concluded that gelatin interfered with plasma vWF, not with platelet-vWF or with platelet GpIb.

The results of clinical trials may differ from *in vitro* studies. In thromboelastograph (TEG) studies, Karoutsos *et al.*[23] revealed no hypocoagulability after moderate doses of gelatin, HES (200/0.5) or albumin (mean doses 1300–1800 ml). They found a hypercoagulability state only after administration of gelatin. Studies in volunteers and *in vitro* studies reproduce poorly the multiple *in vivo* interactions

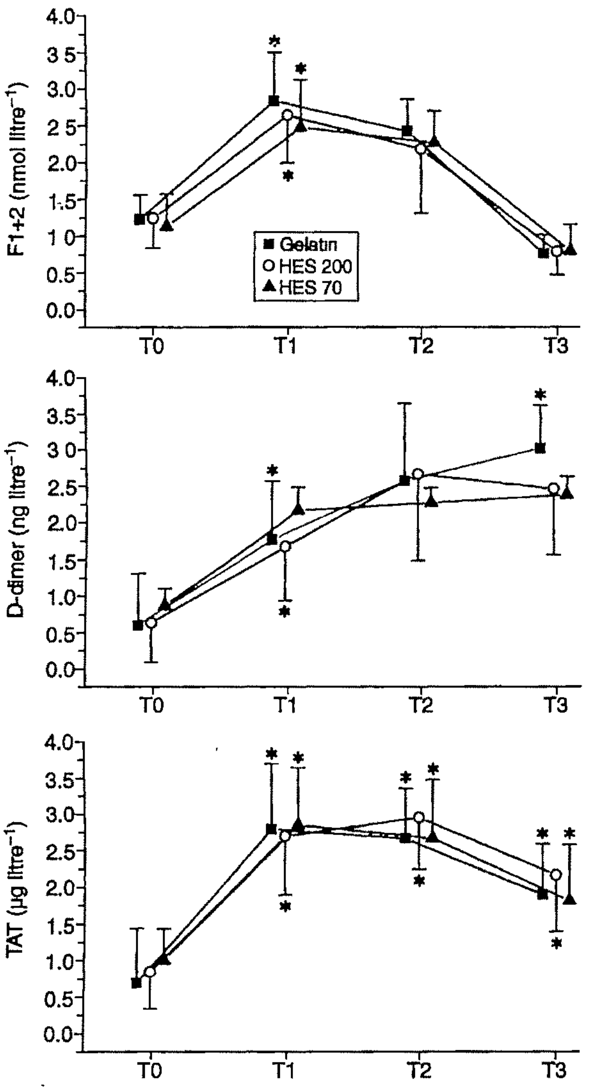

Fig 1 Changes of D-dimer (normal values. <0.5 mg l^{-1}), F1+2 (normal values. <1.0 nmol litre^{-1}), and thrombin/anti-thrombin III complex (TAT; normal values <4.0 μg litre^{-1}) Mean (SD); $^*P<0.05$ different from baseline values T0 (prior to surgery), T1 (end of surgery), T2 (4 h after surgery) and T3 (first postoperative day)

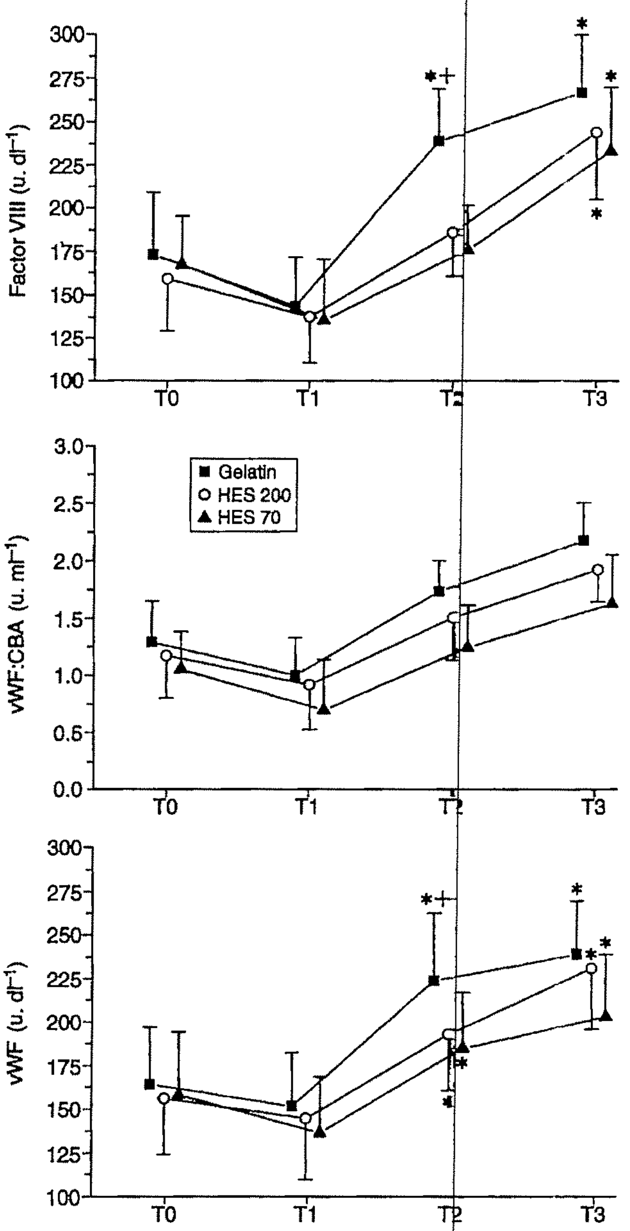

Fig 2 Changes of factor VIII (normal values 60–150 U dl^{-1}), von Willebrand factor (vWF, normal values 60–160 U dl^{-1}), and collagen-binding activity of von Willebrand factor (vWF-CBA, normal values 0.6–1.8 U ml^{-1}). Mean (SD), $^*P<0.05$ different from baseline values, $^+P<0.05$ different to the other groups T0 (prior to surgery), T1 (end of surgery), T2 (4 h after surgery) and T3 (first postoperative day).

leading to coagulation.[23] After surgery, a hypercoagulable state may develop,[10] but in all *in vitro* studies this natural hypercoagulability is absent. In the present study, TAT, F1+2, D-dimer and factor VIII increased significantly during the study period, indicating thrombin generation and reactive hyperfibrinolyis during and after surgery. Hobisch-Hagen and colleagues[24] showed that global tests of coagulation (PT, Quick, aPTT) were only slightly influenced by gelatin used in orthopaedic patients undergoing acute normovolaemic haemodilution. They found, however, increased concentrations of activation markers for coagulation (F1+2), TAT and fibrinolysis (D-dimer). The influence of intravascular volume replacement with synthetic colloids on platelet function is another subject of debate. Infusion of HMW-HES in patients undergoing orthopaedic surgery resulted in a clear 'trend' towards decreased platelet aggregation.[5] In a case report, a reduced level of all three main factor VIII parameters (VIII : C, vWF, vWFag) was found in a patient after infusion of HMW-HES.[25] With reduced VIIIR-RCo there is reduced binding to platelet membrane receptor proteins GPIb and GPIIb/IIIa which results in a decreased platelet adhesion. After large doses of HMW-HES, the platelets appeared swollen and platelet adhesion was reduced.[26] Thurner[27] observed a significant decrease of ristocetin-induced platelet aggregation in gel-

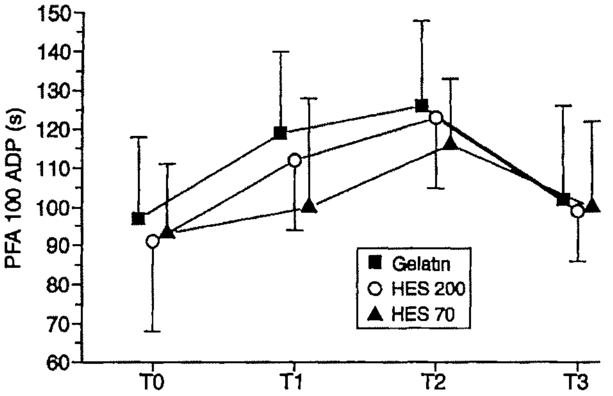

Fig 3 Changes of 'closing time' of the Platelet Function Analyser PFA-100™ using ADP as an inductor (normal values: 77–130 s). Mean (SD); *P<0.05 different to the other group T0 (prior to surgery), T1 (end of surgery), T2 (4 h after surgery) and T3 (first postoperative day)

atin-treated patients, whereas in a HES 200/0.5-treated group, significantly less change in platelet function was found. Evans and co-workers[28] showed that gelatin was associated with varying effects on platelet function: Haemaccel® resulted in more severe disturbances of platelet aggregation than Gelofusine® most likely due to its higher Ca^{2+} concentration. In the present study, we used the PFA-100™ system to assess platelet function. This system uses whole blood and thus provides a more realistic environment to the aggregation of platelets than other tests (e.g. using platelet aggregometry with platelet-rich plasma).[8] The 'closure time' increased slightly during the study, indicating reduced platelet function. This, however, was within the normal range and without differences between the groups. It is summarized that in patients undergoing major abdominal surgery infusing moderate amounts of gelatin, HES 70/0.5 or HES 200/0.5 did not differ with regard to bleeding tendency and use of allogeneic blood. Serially measured molecular markers of haemostasis and indicators of platelet function revealed no relevant differences among the three groups. All three regimens of volume replacement appear to be safe concerning haemostasis in these patients.

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Anaesthesia with propofol decreases FMLP-induced neutrophil respiratory burst but not phagocytosis compared with isoflurane

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Propofol has been reported to produce a dose-dependent inhibition of phagocytosis and superoxide anion production during the respiratory burst (RB) of polymorphonuclear cells (PMNs) *in vitro*. In this randomized, blinded study, these two parameters were compared during propofol or isoflurane anaesthesia in patients undergoing elective interventional embolization of cerebral arterio-venous malformations. Anaesthesia was performed with continuous intravenous propofol 6–8 mg kg^{-1} h^{-1} (n=15) or isoflurane 0.8–1.0% end tidal (n=15). Heparinized blood was drawn before, and 2 and 4 h after induction of anaesthesia. The RB in isolated leucocytes was measured with the fluorescent dye rhodamine after *ex vivo* induction by *Escherichia coli* or tumour necrosis factor α/*N*-formyl-methionyl-leucylphenylalanine (TNF-α/FMLP). Phagocytosis was carried out in whole blood after incubation with fluorescein isothiocyanate (FITC)-labelled, opsonized *E. coli* and also measured with a flow cytometer. The two groups were similar in terms of biometric data and haemodynamic responsiveness. After 4 h of propofol or isoflurane anaesthesia, the mean (SD) phagocytosis of *E. coli* was 93.2% (7.0%) and 94.3% (9.2%), respectively, of that before anaesthesia. The percentage of PMN with RB activity following TNF-α/FMLP stimulation was significantly reduced after 2 h (80.9% (24.2%); P<0.05) and 4 h (53.7% (27.3); P<0.05) of anaesthesia with propofol compared with the values before induction. This effect of propofol anaesthesia was significantly different from the effect of isoflurane anaesthesia. In contrast to published *in vitro* results, 4 h of anaesthesia with propofol did not reduce the phagocytotic capacity of human blood PMN more than isoflurane anaesthesia.

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Polymorphonuclear cells (PMNs) are the first line of defence against bacterial and fungal infections. Their main function is to protect the host by destroying invading micro-organisms. They play a decisive role in the inflammatory process, which may have already been activated intra-operatively by surgical trauma.[1] Therefore, it is feasible that the possible inhibitory effects of anaesthetics on PMN functions may increase the risk posed by microbial infection acquired intra-operatively.

There is evidence that intravenous anaesthetics can influence the immune system.[2] In a previous study, we showed that propofol and its lipid carrier, Intralipid, induce concentration-related inhibition of superoxide anion production during the respiratory burst (RB) of PMNs *in vitro*.[3] The RB enzyme in the plasma membrane of neutrophils catalyses the oxidation of NADPH, leading to the production of superoxide anions which, in turn, is responsible for killing the phagocytosed micro-organisms.[4] Other authors found similar inhibitory *in vitro* effects of propofol on different granulocyte functions.[5–7] Only a few studies have investigated potential immune-compromising effects of intravenous anaesthetics under clinical conditions.[8 9] One reason for this may be the difficulties in differentiating between effects on the immune system associated with the anaesthetic itself or the operative trauma, and other side effects occurring during the operation, such as volume shift, loss of body temperature or infusion of blood components. However, the effects of continuous propofol anaesthesia on blood PMNs are still unknown.

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Table 1 Patient characteristics, amounts of drugs administered, infused volume, urine output, amount of contrast medium and decrease in rectal temperature 4 h after induction of anaesthesia. The consumption of isoflurane was calculated by weighing the isoflurane vaporizer before and at the end of investigation. Results are mean (SD) There were no significant differences between the groups

	Isoflurane	**Propofol**
Gender (male/female)	4/11	8/7
Age (yr)	42.0 (15.5)	35.9 (11.7)
Height (m)	1.72 (0.1)	1.73 (0.1)
Weight (kg)	73.0 (11.3)	73.5 (19.0)
ASA physical status (I/II)	9/6	11/4
Propofol		
induction (mg kg^{-1})	2.78 (1.12)	2.53 (0.76)
continuous (mg kg^{-1} h^{-1})	–	6.25 (1.64)
Isoflurane (g h^{-1})	7.38 (0.95)	–
Atracurium, continuous (mg kg^{-1} h^{-1})	0.47 (0.08)	0.45 (0.05)
Alfentanil (mg h^{-1})	0.43 (0.19)	0.42 (0.31)
Infused volume (ml kg^{-1} h^{-1})	8.07 (2.69)	6.70 (1.99)
Urine output (ml kg^{-1} h^{-1})	4.91 (1.62)	4.11 (1.23)
Contrast medium (ml kg^{-1} h^{-1})	0.43 (0.09)	0.47 (0.16)
Decrease in rectal temperature (°C)	0.15 (0.34)	0.15 (0.32)

Our aim was to evaluate the time-dependent changes in PMN functions during elective interventional neuroradiological procedures with propofol or isoflurane anaesthesia. In this controlled, randomized, blinded study, the induced RB and the phagocytotic capacity of blood PMNs were investigated after 2 and 4 h of general anaesthesia.

Anaesthesia was performed with continuous propofol infusion (1% Disoprivan; Zeneca, Plankstadt, Germany) or isoflurane inhalation (Forene; Abbott, Wiesbaden, Germany). All patients underwent elective interventional neuroradiological procedures for embolization of cerebral arterio-venous malformations (AVM). As the surgical trauma associated with such procedures is minimal compared with that in abdominal or orthopaedic operations, we believe that these procedures are suitable for investigating the potential immune system effects of anaesthetics in humans. Additionally, during embolization there is no significant reduction in body temperature or marked change in blood volume. Infusion of blood components, with possible immune-compromising consequences,[10] is unlikely to be necessary.

Methods

The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all patients. The patients (12 male, 18 female) had a mean age of 38 yr (range 12–67 yr) and an ASA status of I or II (Table 1). All patients suffered from cerebral AVM and underwent elective super-selective embolization under general anaesthesia in the Neuroradiological Department of the Hanover Medical School. Patients taking potential immune-compromising medication, such as steroids or non-steroidal anti-inflammatory medication, were excluded. Since each embolization was elective, no patient presented with a history of acute infection during the 2 weeks before the procedure.

One hour before induction of anaesthesia, all patients were premedicated with oral midazolam. Patients were randomly assigned to anaesthetic maintenance with propofol (n=15) or isoflurane (n=15). Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and alfentanil 15–20 µg kg^{-1}, and oral intubation was carried out after application of atracurium 0.5 mg kg^{-1}. Patients' lungs were mechanically ventilated with 70% nitrous oxide and 30% oxygen with a fresh gas flow of 1 litre min^{-1}. End-expiratory carbon dioxide was maintained between 4.5% and 5%. Continuous propofol infusion (6–8 mg kg^{-1} h^{-1}) or isoflurane inhalation (end-expiratory concentration 0.8–1.0% v/v) was supplemented with a bolus application of alfentanil 5–10 µg kg^{-1} h^{-1}. Continuous relaxation was carried out with atracurium infusion (0.3–0.5 mg kg^{-1} h^{-1}) and monitored with a peripheral nerve stimulator. The train-of-four quotient obtained was <25%. To compensate for baseline fluid consumption, Ringer's lactate 6–8 ml kg^{-1} $h^{-1}$was infused in both groups. Heart rate, peripheral oxygen saturation, arterial and central venous pressure, rectal temperature, end-expiratory isoflurane concentration, carbon dioxide concentration and degree of muscle relaxation were measured and recorded continuously. Amounts of propofol, atracurium and alfentanil administered, infused volume and amount of X-ray contrast medium (Iopromid, Ultravist-240; Schering, Berlin, Germany) and urine output per hour were measured in all patients during the 4 h study period. The consumption of isoflurane was calculated by weighing the isoflurane evaporator before and at the end of the investigation.

Micro-catheterization was performed through an introducer in the femoral artery. After mapping the AVM with digital subtraction angiography, maize protein (Ethibloc occlusion emulsion; Ethicon, Hamburg, Germany) was injected into the feeding vessels.

Sample preparations

Samples (7.5 ml) of venous blood were collected in disposable blood sampling tubes coated with lithium heparin 15 IU ml^{-1} (S-Monovette LH; Sarstedt, Nümbrecht, Germany) before and 2 and 4 h after induction of anaesthesia. After fixing with 3% acetic acid, leucocytes from all samples were counted in a Neubauer cell counting chamber.

Respiratory burst

The protocol of Rothe and colleagues[11 12] was used. NADPH oxidase activity was assayed by measuring the intracellular oxidation of dihydrorhodamine 123 (DHR; MoBiTec, Göttingen, Germany) to the green fluorescent dye rhodamine 123 in a flow cytometer. The assay depends upon the incorporation of DHR into the cell. After cell activation, NADPH oxidase catalyses the reduction of oxygen to superoxide anions which are further transformed by dismutation to hydrogen peroxide. The non-fluorescent DHR is oxidized intracellularly in a peroxidase-dependent reaction to rhodamine 123. The amount of rhodamine 123 is proportional to the hydrogen peroxide generated. To isolate leucocytes, 3 ml of heparinized whole blood was layered on to 3 ml of Ficoll Hypaque (density 1.077 g dl^{-1}; Biochrom, Berlin, Germany). Nucleated blood cells in the supernatant were harvested without centrifugation. To 1 ml of phosphate-buffered saline (PBS) pH 7.2, without Ca^{2+} and $MgCl_2$ (Gibco-BRL, Eggenstein, Germany), heated to 37°C, 30 µl of the leucocyte supernatant (containing an average of 5×10^5 cells ml^{-1}) was added; the mixture was incubated with 15 µl of 1 mM DHR. RB was induced by 20 µl of *Escherichia coli* HB-101 (1×10^9 ml^{-1}; Sigma) or by priming with 10 ng (10 µl of a 1 µg ml^{-1} solution) of recombinant tumour necrosis factor alpha (TNF-α; Sigma) for 5 min followed by receptor stimulation with 10 µl of 0.01 mM *N*-formyl-methionyl-leucylphenylalanine (FMLP; Sigma). After incubation (20 min, 37°C), the reaction was terminated by transferring the samples on to ice. To determine viability, dead cells were counterstained with 1 mM propidium iodide (Serva, Heidelberg, Germany). Samples were stored on ice and subjected to flow cytometry within 30 min (see below). Negative controls without stimulation were included to detect possible preactivation of neutrophils.

Phagocytosis assay

A commercial test kit (Phagotest; Orpegen, Heidelberg, Germany) was used to determine the phagocytotic activity of PMNs. Briefly, 50 µl of heparinized whole blood was incubated (10 min, 37°C) with 5 µl of opsonized and fluorescein isothiocyanate (FITC)-labelled *E. coli* (1×10^9 ml^{-1}). Negative controls were kept on ice. After addition of 50 µl of quenching solution (Orpegen) and 3 ml of PBS, the samples were centrifuged (5 min, 250*g*, 4°C). Fifty microlitres of lysis solution (Optilyse; Immunotech, Krefeld, Germany) was added and the mixture incubated for 10 min. Two millilitres of distilled water was added; the samples were then incubated for another 10 min and centrifuged. After washing of the remaining cell pellet and addition of propidium iodide (50 µl, 1 mM), the samples were analysed by flow cytometry.

Flow cytometry adjustment and acquisition

Both of the flow cytometric assays used allow quantification of PMN responses at the single-cell level. The flow cytometer (Epics XL; Beckman-Coulter, Krefeld, Germany) was equipped with an argon ion laser adjusted to a wavelength of 488 nm. Twenty thousand events were measured for each sample. The rhodamine emission of the RB assay and the FITC emission of the labelled *E. coli* in the phagocytosis test were measured with the photomultiplier in the green fluorescence channel (FL1; 515–545 nm). A photomultiplier for red fluorescence (FL3; 650 nm) was used to measure propidium iodide emission in order to discriminate between living and necrotic cells, or between bacteria and leucocytes. Sideways scatter (SSC) and forward scatter (FSC) were assessed in linear mode, and FL1 and FL3 in logarithmic mode without compensation. The photomultiplier voltage and gains of FSC, SSC, FL1 and FL3 were adjusted for each negative control and remained constant for the matched samples. Data files were stored in list mode and analysed in dot plots using a PC software package (EXPO 2.0; Beckman-Coulter). An example of data processing is shown in Figure 1.

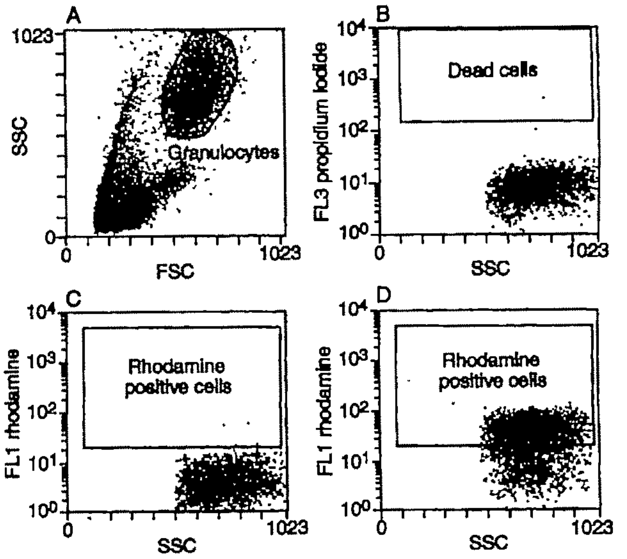

Fig 1 Adjustment of the acquisition dot plots for analysis of the neutrophil respiratory burst due to the green rhodamine fluorescence (A) Forward scatter (FSC) versus sideward scatter signals (SSC) were depicted as acquired on the flow cytometer Neutrophils were localized and gated based on their high SSC signals. Only neutrophils from this region were used in the next dot plot. (B) SSC versus red propidium iodide fluorescence (photomultiplier FL3) for gating of necrotic neutrophils ('dead cells') based on their strong red fluorescence. Cells from this gate were excluded in the following dot plots. (C and D) SSC versus green rhodamine fluorescence (photomultiplier FL1) for gating of rhodamine-positive cells using the gate combination 'granulocytes' of dot plot A but not 'dead cells' of dot plot B. (C) is an example for a negative control without stimulation, whereas (D) depicts RB-positive PMNs after *E. coli* stimulation.

All immune function tests were performed by a single investigator who was blinded to the anaesthetic management.

Statistical analysis

The percentage of activated PMNs (in the RB assay, the percentage of rhodamine-positive PMNs after induction with *E. coli* or TNF-α/FMLP; in the phagocytosis assay, the percentage of PMNs containing FITC-labelled *E. coli*) after 2 and 4 h of anaesthesia with propofol or isoflurane was compared with the percentage before induction of anaesthesia (the latter was set at 100%). This net effect was calculated using the formula:

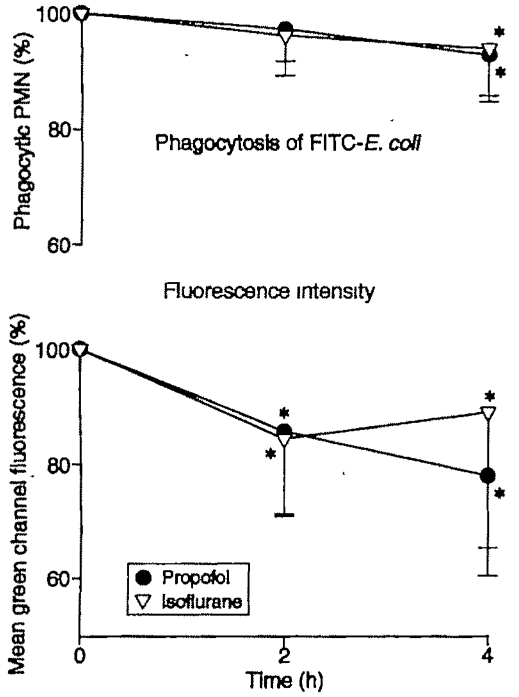

Fig 2 Percentage of PMNs phagocytosing opsonized FITC-labelled *E. coli* (upper panel) and the phagocytic activity in single PMNs expressed by the mean green channel fluorescence (lower panel) in patients given propofol (●) or isoflurane (▽) *Significantly different from values before induction of anaesthesia (100%). There were no significant differences between propofol and isoflurane anaesthesia in either of the phagocytosis parameters tested. Data are expressed as mean – SD.

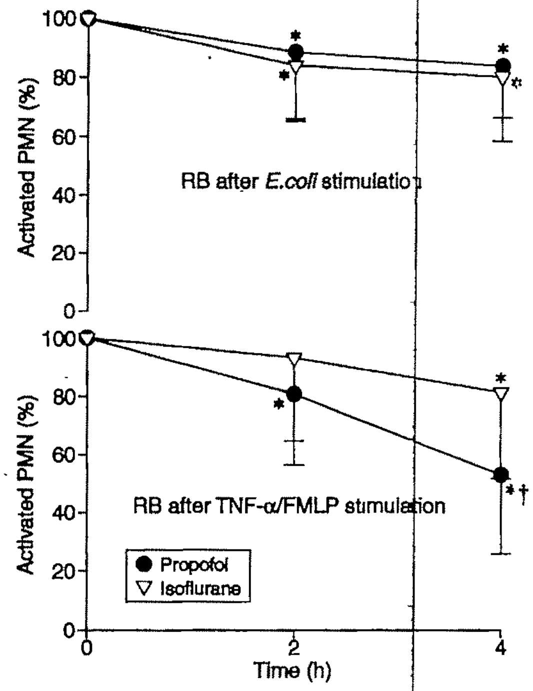

Fig 3 Percentage of PMNs producing superoxide anions during the respiratory burst after stimulation with *E. coli* (upper panel) and TNF-α/FMLP (lower panel) in patients given propofol (●) or isoflurane (▽). *Significantly different from values before induction of anaesthesia (100%) †Significant difference between propofol and isoflurane Data are expressed as mean – SD.

$$\textit{activated PMN \%} = \frac{\textit{positive PMN after anaesthesia}\,(2\,h,\,4\,h)}{\textit{positive PMN before anaesthesia}} \times 100\%$$

Results are presented as mean (SD). The phagocytotic activity of PMNs is also expressed as the percentage of mean green channel fluorescence per cell. Time-dependent intragroup data were evaluated using a two-tailed, paired *t*-test. At each time, differences between propofol and isoflurane were evaluated using one-factor (group) analysis of variance (ANOVA) for repeated measurement, followed by Student–Newmann–Keuls multiple comparison test. $P<0.05$ was considered significant.

Results

There were no significant differences between the two groups in terms of patient characteristics, the amount of alfentanil or atracurium administered, the infused volume or the amount of contrast medium used after induction of anaesthesia during the 4 h study period (Table 1).

There were no significant differences in the intraoperative parameters of pulmonary and circulatory function (peripheral oxygen saturation, end-expiratory carbon dioxide concentration, heart rate or arterial and central venous pressure; data not shown) or in decrease in rectal temperature and urine output (Table 1).

The number of leucocytes increased in both groups during the investigation period: at 0, 2 and 4 h of propofol anaesthesia there were 4.1 (2.0), 4.7 (3.3) and 5.3 (3.2) × 10^6 ml^{-1} leucocytes, respectively; the corresponding values for isoflurane anaesthesia were 4.2 (2.8), 4.7 (2.4) and 5.0 (2.4) ×10^6 leucocytes ml^{-1}. There was no significant difference between the groups. The percentage of propidium iodide-positive PMNs, used as a measure of cell necrosis, was low (<5%) in both groups throughout the investigation period.

After 4 h of anaesthesia, the percentage of phagocytic PMNs that were ingesting opsonized FITC-labelled *E coli* was slightly lower (propofol: 93.2% (7.0%), $P=0.02$; isoflurane: 94.3% (9.2%); $P=0.03$) than before induction of anaesthesia (Figure 2). The phagocytotic activity of each single cell expressed by the mean channel green FITC fluorescence was also reduced in both groups (propofol: 78.4% (12.7%), $P<0.001$; isoflurane: 89.4% (28.6%), $P=0.002$). There was no significant difference between propofol and isoflurane anaesthesia in either measure of phagocytosis (Figure 2).

The percentage of PMNs with RB activity after stimulation with *E. coli* was reduced during anaesthesia, but without significant difference between the two groups (Figure 3). RB activity induced by TNF-α/FMLP was

54% lower ($P<0.001$) after 4 h of anaesthesia with propofol than it was before induction of anaesthesia. In PMNs in patients given isoflurane for the same length of time, RB activity was reduced by 18% ($P=0.031$). The difference between the propofol and isoflurane groups was significant ($P=0.011$) (Figure 3). Linear regression analysis also showed a significant time-dependent reduction in TNF-α/FMLP induced RB activity ($r=0.48$, $P=0.008$) under propofol anaesthesia. The power with $\alpha=0.05$ was 0.84, which means there is a 16% chance (β error) that the observed difference between propofol and isoflurane is not significant.

Discussion

The essential role in host defence of phagocytosis and production of superoxide anions during the RB is illustrated by the marked propensity of patients with certain clinical deficiency syndromes like chronic granulomatous disease or congenital disorders of phagocytic activity, to develop infections.[13] Phagocytosis and superoxide anion production are mainly responsible for bacterial killing of PMNs. So if anaesthetics were to suppress these functions, this could reduce host defence. We investigated phagocytosis and RB activity during propofol or isoflurane anaesthesia in patients undergoing elective interventional embolization of cerebral AVM.

Phagocytosis

We found a significant reduction in the number of blood PMNs with phagocytotic activity and in the phagocytotic capacity of each single PMN during propofol or isoflurane anaesthesia. It has been shown previously that phagocytosis by blood cells is reduced after anaesthesia and surgery.[14 15] Reduced phagocytosis seems to be associated with general anaesthesia as demonstrated by Hole, Unsgaard and Breivik,[15] who showed that a decrease in phagocytosis was caused by general anaesthesia but not by epidural anaesthesia.

Recently, Kotani and co-workers reported that the phagocytic capacity of alveolar macrophages decreased during anaesthesia with isoflurane or propofol.[16] These findings are complementary to our findings of reduced phagocytosis by blood PMNs after 2 and 4 h of propofol or isoflurane anaesthesia. In both types of anaesthesia, RB activation via viable, non-opsonized *E. coli* and phagocytosis of opsonized FITC-labelled *E. coli* were significantly depressed. We can, thus, add to the findings of Kotani *et al.* by showing that, under general anaesthesia, opsonin-dependent and opsonin-independent phagocytosis is reduced not only in alveolar macrophages but also in blood PMNs. In neither study was this effect dependent on the anaesthetic used; rather, it seems to depend on the conditions of general anaesthesia itself.

Our most notable finding was that propofol anaesthesia did not cause a greater reduction in the phagocytic activity of blood PMNs than isoflurane anaesthesia, as might have been expected from published *in vitro* results. In two *in vitro* studies carried out with the same flow cytometric phagocytosis assay applied in the present study, marked inhibition of neutrophil phagocytosis has been demonstrated after incubation with clinically relevant concentrations of propofol.[5 17] In both studies the inhibition by propofol was concentration-related. Should this marked *in vitro* inhibition of phagocytosis by propofol also take place under clinical settings, e.g. after sedation of ICU patients with propofol for several days, this would probably result in reduced microbial killing and an increased risk of infection induced by propofol. In fact, we were unable to show a significant difference in inhibition of PMN phagocytotic capacity after 4 h of intravenous propofol anaesthesia which is, of course, a short time compared with sedation on ICU.

Respiratory burst

In the present study, the RB was measured after challenge with two different stimuli in order to discriminate between phagocytosis- and receptor-dependent activation of RB. The former was carried out assayed by stimulation with phagocytosis of *E. coli* and the latter by receptor activation with the bacterial peptide FMLP after priming with TNF-α. Both pathways increase the intracellular Ca^{2+} content which activates protein kinase C (PKC) and, hence, NADPH oxidase.[4] Inhibition of the RB was estimated from the reduction in the number of PMNs recruited for the RB (percentage of activated PMNs).

The bacterial peptide FMLP is an agonist which mediates the response to bacterial formyl products in the inflammatory environment via a specific formyl peptide receptor on the cell surface. The receptor mediates multiple responses, including chemotaxis, exocytosis of certain enzymes, generation of superoxide anions by the NADPH oxidase complex during the RB and phagocytosis of *E. coli.*[18 19] Like other 'classical' chemoattractant receptors (e.g. complement factor C5a, platelet activating factor (PAF) or lipopolysaccharide (LPS)), the FMLP receptor is linked to a heterotrimeric G protein, leading via intermediate steps to activation of PKC which, in turn, activates NADPH oxidase.[20] Priming with cytokines such as TNF-α before FMLP activation leads to a high proportion of PMNs being activated. Priming is defined as the exposure of cells to a triggering agent, so that there is a markedly increased response to a second stimulus.[21] It has been suggested that priming with TNF-α increases neutrophil FMLP receptor expression.[22 23]

We found that anaesthesia with propofol, but not isoflurane, decreased RB activity after isolated blood PMNs had been primed with TNF-α, followed by FMLP stimulation. This finding is in accordance with the results of Nakagawara and colleagues, who demonstrated that volatile anaesthetics do not seem to interfere with the FMLP receptor, because the affinity of the FMLP receptor for radiolabelled FMLP was not altered in the presence of volatile anaesthetics.[24] An *in vitro* study has demonstrated that isoflurane under clinically relevant concentrations had no effect on FMLP-stimulated RB.[25] This study, in particular, was carried out with the same flow cytometry method used in our investigation. The results of the present study and of both cited studies emphasize that isoflurane anaesthesia seems to have only minor effects on the RB of human blood PMNs. In contrast to isoflurane, anaesthesia with propofol seems to interfere with the FMLP receptor or downstream regulation of PMNs. Further studies are necessary to confirm this hypothesis.

In vitro effects of propofol

It is probable that the reported *in vitro* effects of propofol are caused mainly by its lipid carrier, Intralipid, a long-chain triglyceride (LCT) solution which produces concentration-dependent inhibition of different leucocyte functions *in vitro*.[26] In this previous study we showed that LCT lipids inhibit the RB, whereas a mixture of LCT and saturated medium-chain triglycerides (MCT) augments the RB. In a recent *in vitro* study, we found that a new propofol preparation dissolved in LCT/MCT lipid (Propofol Lipuro; B. Braun, Melsungen, Germany) gave similar results to standard LCT propofol (Disoprivan; Zeneca).[17] It is known that polyunsaturated fatty acids like LCT can be rapidly incorporated into cell membranes,[27] thereby increasing membrane rigidity.[28] Thus, propofol could inhibit the RB because of a direct effect of its lipid carrier, LCT, on NADPH oxidase in the plasma membrane of PMNs. NADPH oxidase has at least six components. In the resting cell, three of these components are in the cytosol and three in the plasma membrane. After activation by PKC, all components combine in the plasma membrane to produce a fully functional enzyme complex.[4] The increase in membrane rigidity following incubation with LCT *in vitro* could explain the delayed formation of the NADPH oxidase enzyme complex as well as the inhibition of phagocytosis. The close contact between few non-circulating PMNs and fat over an incubation period of at least 20 min. Results in rapid incorporation of LCT fat into the cell membrane could explain the *in vitro* suppression of the RB and phagocytosis after incubation with LCT–propofol and LCT alone.

Other potential influences

When investigating the effect of anaesthesia on immune function, it is very important to estimate the influence of independent contributions such as operative trauma, mechanical ventilation, co-medication, temperature loss, volume shift or transfusion of blood components. All of our patients were subjected to the same time-dependent alterations of immune function induced by general anaesthesia, mechanical ventilation and embolization of cerebral AVM. In our clinical setting, we attempted to keep these interferences to a minimum. Each embolization was elective, and none of our patients was on steroid or non-steroidal anti-inflammatory medication known to interfere with PMN functions and viability.[29] We believe that it is safe to assume that the trauma-induced effects, on immune cells, of interventional embolization of cerebral AVMs is only minor compared with the effects of surgical procedures. Furthermore, the patients in our study did not have significant reduction in body temperature, which has been shown to reduce the release of TNF-α and interleukin-1β.[30] Radiographic contrast medium reduces the percentage of granulocytes involved in phagocytosing *E. coli* but not the number of pathogenic bacteria.[31] Furthermore, the impairment was most pronounced immediately after the injection of radiographic contrast medium and then rapidly returned to baseline.[32] In the present investigation, a possible influence of contrast medium cannot be excluded, but there was no significant difference between the two groups in the amount of contrast medium administered, so any effect of the medium should have been equal in the two groups.

In conclusion, the phagocytotic activity of blood PMNs decreased significantly during the investigation period for both of the anaesthetics studied. Production of superoxide anions after FMLP activation was markedly lower during propofol anaesthesia than during isoflurane anaesthesia, suggesting that 4 h propofol anaesthesia may reduce FMLP receptor expression on the PMN surface. Additional investigations are necessary to test the hypothesis that propofol interferes with the FMLP receptor or the downstream regulation of human PMNs.

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LABORATORY INVESTIGATIONS

Somatosensory evoked potentials for closed-loop control of anaesthetic depth using propofol in the urethane-anaesthetized rat

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Primary somatosensory cortical mass responses have been shown to exhibit dose-dependent changes in latency when general anaesthetics are administered. Here we describe a system in which the latency of evoked responses was measured automatically in real time in five animals. Latency changes were used to operate a closed-loop control of propofol delivery by intravenous infusion. The system attempted to induce and maintain a 1 ms increase in evoked response latency; this was reversed when infusion was discontinued. Allowing for the rapid and large biological fluctuations in the evoked response, this was achieved successfully. The system maintained a mean increase in latency of 1.27 (SD 0.42) ms. The mean statistical dispersion index of data obtained during the controlled period was 1.23 (0.3); in an ideal controllable system it approximates to 1. Such a system may provide a means for the automatic delivery of anaesthetics.

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Closed-loop control of the delivery of anaesthetic drugs offers the prospect of anaesthetic administration which is precisely matched to the anaesthetic requirements of the patient on a moment-by-moment basis. Systems of closed-loop control depend upon measuring an index of anaesthetic depth in real time so that alterations in the neurological state of the subject can be matched by appropriate alterations in the rate of delivery of anaesthetic drugs. The purpose of this study was to design and implement a system of closed-loop control based on real-time measurement of evoked potential latency, which is used as an index of anaesthetic depth.

Various strategies have been employed in attempts to develop systems of feedback control in anaesthesia. Some studies have investigated the use of the electroencephalogram[1] or its derivatives,[2–6] but signal processing and electroencephalographic pattern analysis have proved complex and difficult. An alternative approach has been the use of auditory evoked potentials for anaesthetic monitoring and control.[7 8] Likewise, somatosensory evoked potentials show progressive changes with alterations in the depth of anaesthesia.[9 10] The absence of appropriate techniques for estimating rapidly and reliably the diagnostic components of evoked responses has, however, led to their use being confined to off-line anaesthesia analysis and to neurological diagnostic tests; they are never used in the control of anaesthesia in real time.

We have developed a system which obtains reliably an estimate of moment-by-moment changes in the latency of the somatosensory evoked response. Using a process of proportional–integral (PI) control, the system executes instantaneous adjustments to the rate of delivery of intravenous propofol. Once the operator has defined a desirable anaesthetic end-point, in terms of altered evoked response latency, the system is able, through closed-loop feedback, to maintain this end-point reliably until instructed otherwise. This technique contrasts both with semi-automated methods of control, such as target-controlled infusion (TCI), and with the step-down manual approach to propofol administration. These latter techniques are open-loop methods derived from

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population-average pharmacokinetic data; they are crucially reliant upon modifications made by the anaesthetist in each individual case. In our closed-loop system, the anaesthetic state is monitored continuously and the rate of delivery of drugs is matched to the precise requirements of the subject. In addition, the burden of repetitious manual evaluation of the depth of anaesthesia is much reduced, and a continuously updated graphical display of changing evoked response indices provides an easily appreciable measure of the depth of anaesthesia of the subject.

Materials and methods

Experiments were performed in accordance with Project Licence PPL 40/1965 issued under the United Kingdom Animals (Scientific Procedures) Act 1986.

Experiments were conducted consecutively after the control system had been properly validated and any programming problems had been eliminated. Initial pilot trials included calibration of the infusion pump and tuning of the PI control parameters (see below). Subsequently, a series of five experiments was undertaken because, in experiments examining anaesthetic mechanisms, a sample of this size is usually sufficient to elucidate neurophysiological effects.

Surgical procedures

Five female albino Wistar rats of the Sheffield strain, in the weight range 190–210 g, were anaesthetized by intraperitoneal injection of 1.25–1.5 g kg^{-1} of urethane 25% (ethyl carbamate; Sigma-Aldrich, Poole, UK) in saline 0.9% without premedication. Tracheotomy was performed and the left external jugular vein was cannulated with PP30 polythene tubing (Portex, Hythe, UK) containing 0.9% saline. The foramen magnum was opened and the arch of the first cervical vertebra was removed, exposing the dorsal surface of the medulla. An extensive craniotomy was performed and the dura mater was reflected to expose the surface of the left cerebral hemisphere. No signs of cortical surface damage or of cerebral oedema were observed in any animal. The animal was suspended in a stereotaxic frame and a liquid paraffin pool was formed over the surface of the brain. The animal's body temperature was maintained at 37.5±0.5°C.

Stimulation

Somatosensory mass responses were evoked, five times per second, by percutaneous electrical stimulation of the contralateral forepaw using 0–100 V square-wave pulses of 100 μs duration (Mark IV isolated stimulator; Devices Ltd, Welwyn Garden City, UK). Stimuli of sufficient intensity to activate Group A fibres supramaximally were delivered.

Recording

Cortical mass responses were recorded via a pair of silver wire electrodes which were fused at their tips to form small balls of approximately 0.5 mm diameter. One electrode was placed gently in contact with the surface of the primary somatosensory receiving area, the other in contact with the surface of the occipital cortex. Mass responses, amplified and filtered with a bandpass of 0.5 Hz–2 kHz, were visualized on a cathode ray oscilloscope and were digitized at 25 kHz. On-line averaging and analysis were performed using a microcomputer running locally written software, which is described below. A common timing pulse was used to trigger the stimulator, oscilloscope and microcomputer. Average evoked responses of 30 individual responses were calculated, thus providing a sampling period of 6 s for signal processing and control.

Administration of drugs

Anaesthesia was induced and maintained by administration of a single dose of urethane. Neurophysiological recording did not commence until at least 1 h after the completion of surgery. Before neurophysiological recording commenced, the majority of the saline in the intravenous cannula was displaced with propofol emulsion 10 mg ml^{-1} (Diprivan; Zeneca, Macclesfield, UK). Care was taken to ensure that propofol was not administered inadvertently to the animal at this stage of the experiment. The propofol-containing syringe was mounted in a Harvard variable-speed infusion pump (Harvard Apparatus, Edenbridge, UK), which was modified to allow control of the infusion rate by a microcomputer.

After a 50 min period of recording under urethane anaesthesia alone, the closed-loop control system was instructed to administer propofol so as to achieve and maintain a 1 ms increase in the latency of the somatosensory evoked potentials. After an 80 min period, during which this latency increase was maintained, propofol administration was discontinued and recording continued for a further period of 110 min to allow complete recovery to the baseline. In no experiment did the animal receive a total volume of propofol of more than 0.9 ml.

Automatic measurement of somatosensory evoked potentials and infusion of propofol

In each experiment, the analysis program obtained an initial average response, which it used as a template against which all subsequent average responses were compared. The first positive inflection in the somatosensory evoked potential always exists, regardless of the shape of the onset and the first positive peak. As illustrated in Fig. 1, the time difference, or latency change, between two averages was measured by shifting the estimation average towards the template average, to arrive at a maximum match along the two inflections. The inflection is represented as a regression model with the peak as a seed point for model inference. The peak of the first positive inflection was localized with a feature-extraction engine which is a composite of wavelet transforms, geometric analysis, artificial intelligence and mathematical analysis. For each subsequent response, the change in latency, compared with that of the template response, was calculated.

After an initial control period, the program was instructed to infuse sufficient propofol to achieve and maintain a 1 ms increase in the latency. The control parameters of the infusion were determined by the results of prior modelling and simulation and the use of data from pilot experiments. The same control parameters were used for all five animals in this study and were unchanged during the course of automatic control. The set-point of the controller was adjusted to reflect the desired latency increase. By continuous comparison of new data for the onset latency of the evoked potential with this new set-point, the controller undertook continuous change in the rate of delivery of propofol using the PI control algorithm. PI control was adopted because of the simplicity of tuning the control parameters on-line, as there were no adequate models for the control of propofol anaesthesia with somatosensory evoked potential as the feedback variable. Thus, at the beginning of the infusion period there was a large discrepancy between the desired latency change and the actual latency change, with the result that propofol was infused at a high rate. This rate was restricted by an infusion rate-limiter incorporated in the controller to prevent overdose. The rate limit was based on experimental values determined in pilot experiments. When values of actual latency change became closer to the desired latency change, the rate of infusion was lowered and was balanced continuously against any small discrepancies which arose during the remainder of the infusion period. Through this process, an elevated onset latency was maintained until the set-point change was returned to its control level and the animal was allowed to recover. Implementation of the control system is described in Fig. 2.

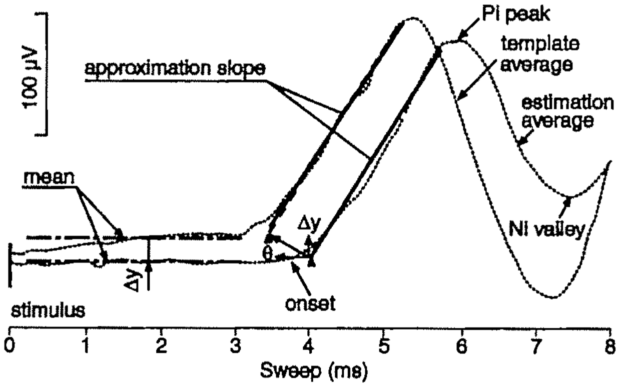

Fig 1 The technique of inflection latency estimation. Two successive average evoked responses are shown by dotted lines. Upon these are superimposed solid lines to show the inflection models which were mathematically derived from the biological data. Dashed lines show the inflection model of the average after being shifted (θ, Δy) towards the template. It is the extent of this shift which provides the index for changing latency between averages. Reproduced from Angel *et al.*,[27] with permission.

Results

Somatosensory mass evoked responses

Electrical stimulation of the contralateral forepaw was followed, with a latency of approximately 4 ms, by a characteristic series of inflections in the potential recorded from the surface of the primary somatosensory cortical receiving area. These inflections were of large amplitude (approximately 100 µV to the peak of the first inflection), were easily measurable, and had a clearly defined onset latency.

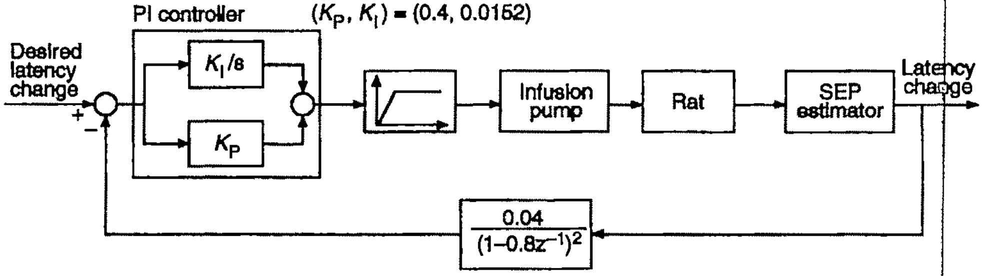

Fig 2 Block diagram to show the drug delivery control system. All system parameters (i.e. of the PI controller, level limiter and filter) are adjustable in real time. The infusion pump is driven by analogue voltage commands and has two ramp modes, mm h^{-1} and mm min^{-1}, with a resolution of 1 ramp unit. An appropriate ramp mode is selected by the pump driver according to the calculated infusion rate. The drug delivery control system was encapsulated as an additional module to an electrophysiological data acquisition system developed in Sheffield[28] The overall system was implemented using the C++ language (Visual C++ v2.2, Microsoft, USA) based on the object-oriented programming technique, on personal computers running Windows 95. System operations were performed via a friendly graphic user interface with both hot keys and a mouse. Only the latency change was used as a feedback variable; however, other diagnostic components of the somatosensory evoked potential were also displayed.

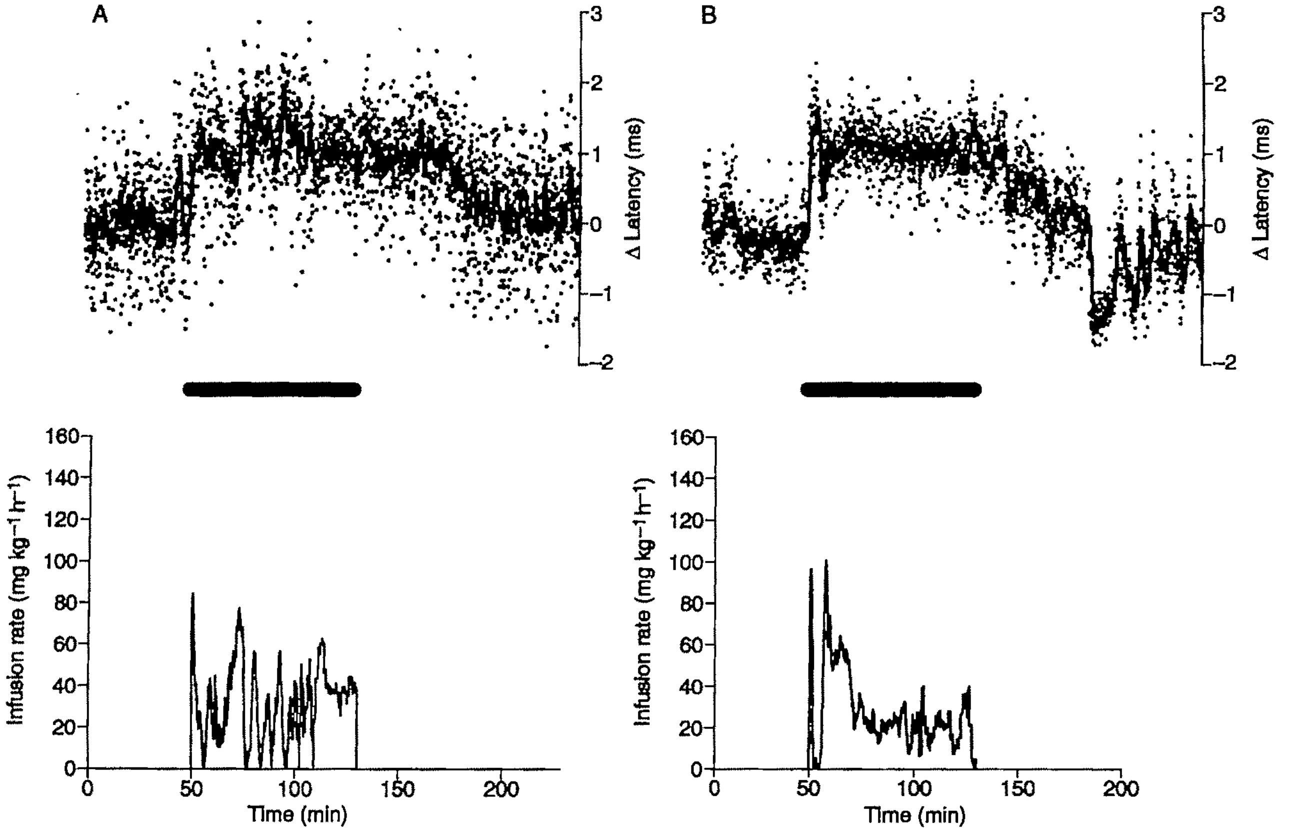

Fig 3 Records of the latency changes which were recorded in two of the animals in the study (A) Data taken from an animal exhibiting a large degree of spontaneous fluctuation in its responsiveness The upper panel shows the raw data obtained by measurement of changing latency (grey dots), upon which is superimposed the smoothed values of latency change which were calculated on-line and which were used by the controller in regulating infusion rate The rapid onset of the effect of propofol is apparent, as is the period of gradual recovery which followed the cessation of infusion. The period during which the controller was instructed to induce a 1 ms increase in the latency, compared with that measured in the control period, is indicated by the horizontal black bar The lower panel shows the rate of infusion of propofol 10 mg ml^{-1} i.v. under closed-loop control. The mean rate of administration, over the whole of the controlled period, was 32 mg kg^{-1} h^{-1}. (B) Similar data taken from an animal which exhibited less spontaneous fluctuation in its responsiveness to the stimulus The narrower scattering in the grey dots, which represent the raw data, is evident. Again, the superimposed line shows the smoothed values for latency change which were used in regulating the infusion rate. The lower panel shows the rate of infusion of propofol during the experiment, which had a mean rate of 27 6 mg kg^{-1} h^{-1} in this animal.

Closed-loop control of propofol infusion

In a series of five experiments, the desired prolonged increase in latency, followed by recovery to baseline values, was attained. Figure 3 shows records obtained in two of the animals in our sample. These two examples were chosen because they illustrate the difference in the extent of spontaneous fluctuation in the latency of response that occurs between animals. The pattern of controlled infusion of propofol under each set of conditions is also shown. In each case, the initial period under urethane anaesthesia alone was associated with a constant mean latency change about which small fluctuations occurred. The extent of this fluctuation varied between animals but is characteristic of animals anaesthetized with urethane[11] or halothane.[12]

The onset of infusion of propofol was associated with a rapid rise in the latency of responses measured in each animal. In each animal, the controller soon discontinued infusion owing to overshoot in the latency change beyond the desired set-point. As the latency of response began to recover, the controller then recommenced infusion so as to catch the latency and maintain it at the set-point. In each animal, the controller then followed a unique pattern of propofol infusion in response to changes in the latency of evoked responses. The pattern was commonly an oscillation in infusion rate in response to fluctuation in the biological responses about the desired set-point or, possibly, a result of inadequate tuning of the control parameters. In one of the animals (Fig. 4) the latency change showed an unexpected excursion from the set-point approximately 40 min after the beginning of the infusion period. This unusual example illustrates the fast response of the controller in causing a rapid but short-lived increase in infusion rate, resulting in the return of the latency change to the set-point. Thus, the infusion rate was matched to changes in the latency of the

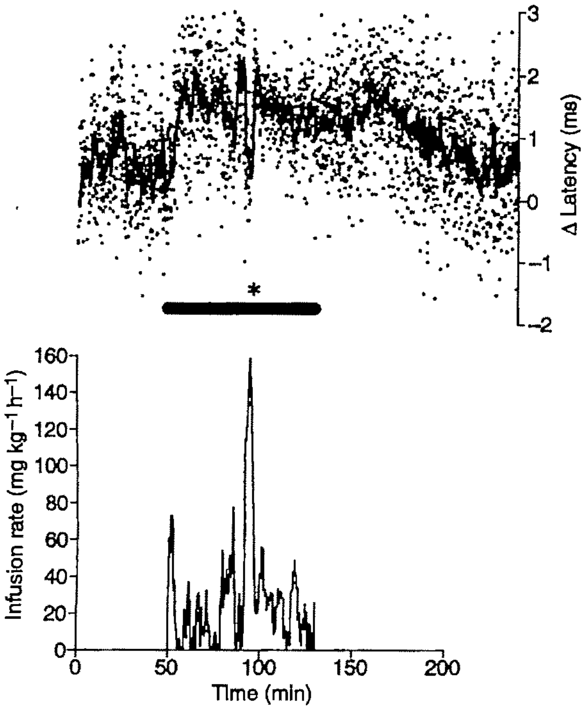

Fig 4 Plots similar to those obtained from the two animals which are represented in Fig 3 Of interest is the excursion from the latency change set-point which occurred approximately 40 min after the beginning of the infusion period (asterisk). The rapid response of the controller (lower panel) in acting to restore the set-point through an increased rate of infusion is shown

evoked potential. In each animal, the cessation of infusion was associated with a gradual recovery in the latency of the evoked response until the control level was restored.

Figure 5 shows the mean latency changes recorded in our sample. The initial period of recording was associated with a stable baseline from which there was a stepped increase in latency when the administration of propofol commenced. This increase was maintained until the delivery of propofol was deliberately discontinued, after which baseline conditions returned gradually.

The cumulative sum (cusum) technique was developed originally to facilitate the analysis of industrial quality control data;[13] it facilitates the appreciation of changes in the average level of a set of sequentially obtained data. Assessment of the performance of the controller in closed-loop control of the depth of anaesthesia is essentially a problem of quality control. Application of the cusum technique has allowed us to gauge easily the extent to which the controller achieved and maintained desired changes in the latency of the somatosensory evoked response. Horizontal portions of the cusum curve reflect periods in which collected data differ little from a predetermined set-point; more rapidly changing portions of the curve correspond to periods during which deviation from the set-point occurs. Figure 5 shows a cusum plot drawn using the mean values obtained from our sample. The comparison level is taken as the mean latency at the start of the recording period. Controlled infusion of propofol was associated with a constant deviation from this level; this is reflected in a diverging portion of the curve in which the constant new gradient reflects the consistent deviation. Discontinuation of infusion was associated with the gradual recovery (60 min in comparison with 23 min after administration of a bolus of propofol)[10] of the animals. Recovery is seen in the gradual return of the gradient of the cusum curve towards the horizontal gradient obtained using data from the control period; thus the gradient of the plot is related to the extent to which mean data deviate from the comparison level.

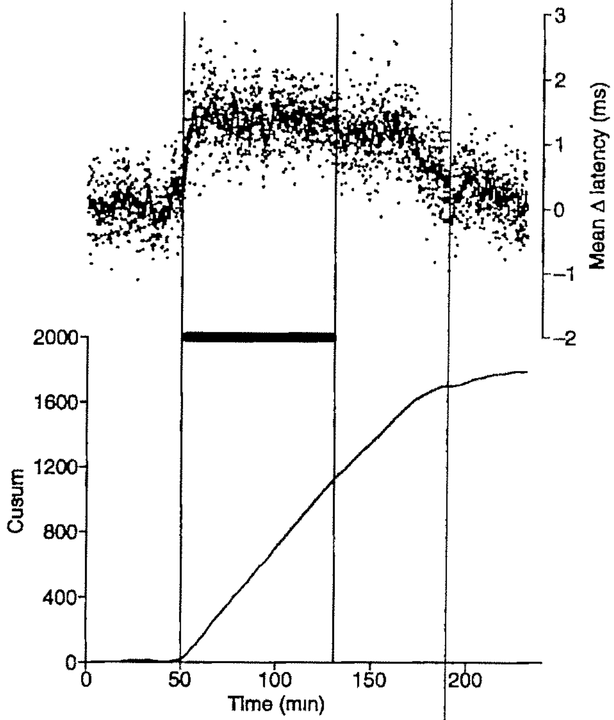

Fig 5 Mean values of latency change which were recorded in our animals (n=5) are shown in the upper panel. The black curve represents the smoothed data, as in Figs 3 and 4, which are superimposed upon the raw mean values obtained every 6 s during the experiment (grey dots) The period of infusion of propofol is indicated by the vertical lines and the horizontal black bar The lower panel shows the cusum plot constructed from these raw mean data. Periods in which measured values differed little from those at the start of the experiment are reflected in horizontal portions of the cusum plot When values differed from this comparison level, these differences were cumulatively summed to yield a portion of the curve which shows an increased gradient When propofol infusion was discontinued, the animals commenced gradual recovery such that the rate of change in the cumulatively summed differences declined Thus, as the animals recovered, the gradient of the cusum plot gradually returns to horizontal The stability of the increased latency that was induced by the controller is reflected in the unchanging gradient in the portion of the cusum plot corresponding to the period of propofol infusion Note that the cusum plot has units of milliseconds, but these are not meaningful in this type of representation.

The success of the system may be evaluated using statistical methods. The performance of the control system is indicated using a statistical steady-state error defined as

Table 1 Performance of the PI control system. Fig. refers to the figure illustrating data from individual animals. SP=set-point, σ_b=standard deviation of the baseline; μ_c=mean latency in the controlled period; σ_c=standard deviation in the controlled period; $E_{SS}\%$=statistical steady-state error; σ_d=statistical dispersion index. For a stable and controllable system, σ_d should approximate to 1. Responses in the controlled period are strongly governed by the controller if σ_d is less than 1

Experiment	Fig.	SP (ms)	σ_b	μ_c	σ_c	$E_{SS}\%$	σ_d
1	4	1.0	0.6157	1.4227	0.6913	42.27	1.1228
2	3A	1.0	0.6205	1.0381	0.5734	3.81	0.9241
3	–	1.0	1.3138	1.9046	1.5023	90.46	1.1435
4	3B	1.0	0.2904	0.8284	0.4979	17.16	1.7145
5	–	1.0	0.8257	1.1286	1.0466	12.86	1.2675

$$E_{SS}=(\mu_C-SP)/SP \qquad (1)$$

and a statistical dispersion index

$$\sigma_d=\sigma_c / \sigma_b \qquad (2)$$

where the mean value μ defines the central tendency of a time series $\{y(t)\}$ and the standard deviation σ defines the dispersion of $\{y(t)\}$, the subscript 'c' representing the controlled period and 'b' the baseline period; SP is the set-point. For a good control session, the mean value μ should overlap the set-point at a maximum coincidence with a certain level of variance (σ^2). For a stable or an asymptotically stable system, the system output should cease oscillation when the system becomes stable. Thus, the dispersion variable σ can be used as an index in measuring how stable and controllable the system is.

The variable $E_{SS}\%$ was used as an index of how well integral control performed, while σ_d describes the dispersion of the controlled responses (governed by proportional control) relative to the baseline. In a stable and controllable system, σ_d approximates to 1, meaning that the controlled period oscillates at an intensity similar to the baseline period. A controller is said to have good performance when σ_d is less than 1 and, hence, where it achieves less oscillation than is seen during the uncontrolled period.

Results from the five experiments which are reported here are given in Table 1. Although the control system was able to track the set-point, there were significant steady-state errors in each experiment. This occurred because control parameter values were fixed across the five experiments and hence were not optimized for each individual animal.

Discussion

In common with the results of previous experiments in the rat, propofol increased the latency of the somatosensory evoked response. Our automated system of infusion control, using the results of on-line measurement of changes in the latency of response, successfully induced and maintained an increase in response latency under closed-loop control. When propofol administration was discontinued, the latency gradually returned to preinfusion values; we speculate that the slowness of the recovery was a consequence of the non-brain tissue of our animals acting as a reservoir of propofol after an extended period of its administration.

Use of somatosensory mass evoked responses

Mass responses recorded from the cortical surface following electrical stimulation of the contralateral forepaw have been suggested to result from the transmission of information in the dorsal column medial lemniscal pathway. The size of the responses has been suggested to reflect the magnitude of the thalamocortical afferent volley and the activation of cortical neurons (reviewed by Angel[14]). The administration of all general anaesthetics which have been tested has been found to cause a dose-dependent increase in the onset latency of the evoked potential.[15] Likewise, the imposition of noxious stimuli or the administration of stimulant drugs is associated with a reduction in the latency. Changes in the onset latency thus provide an index of the action of anaesthesia on the transfer of information in the dorsal column pathway and, by implication, of the depth of anaesthesia.

The cortical responses which we measured have been shown in previous studies to result from the transmission of touch/pressure-type proprioceptive information rather than from the transmission of information related to pain: cortical evoked responses disappear after lesion of the dorsal columns of the spinal cord.[16] The vast majority of cells which are activated by electrical stimulation have small, spot-like peripheral receptive fields on the contralateral forepaw and, are activated by touch, pressure and claw and hair movement.[17] The latency of the evoked response in the unanaesthetized rat is 3.5 ms,[14] which, assuming a synaptic delay of 0.8 ms,[18] leaves $3.5-(0.8\times2)=1.9$ ms for conduction from the wrist to the cortex. The total length of this path was approximately 140 mm in our animals, suggesting a conduction velocity of approximately 74 m s^{-1}. This value is considerably higher than the maximum conduction velocity of 30 m s^{-1} which has been observed in 'fast pain' A∂ fibres. Thus, on the basis of the spinal cord location of afferent fibres, their peripheral receptive field properties and the speed of conduction in the ascending pathway, the cortical evoked responses reflect activity in the tactile, rather than the nociceptive or thermal, sensory afferent pathways.

Effects of urethane anaesthesia on somatosensory evoked responses

Urethane anaesthesia was used in this study because it provides good surgical anaesthesia, has an extremely long half-life and has little cardiovascular or respiratory effect.[19] It has been found to provide a stable baseline upon which to test the neuronal effects of other general anaesthetic drugs.[14] Previous experiments in this laboratory have demonstrated the precise agreement, in terms of the direction and magnitude of anaesthetic-induced perturbation in somatosensory evoked responses, between results obtained in studies in urethane-anaesthetized animals and those from experiments in chronically implanted, initially conscious animals.[20] The effects of propofol that were observed in this study are likely, therefore, to mirror those which would be obtained in an initially conscious animal.

Choice of propofol for this study

Several studies have demonstrated recently the advantages of anaesthesia in which the anaesthetic state is maintained by intravenous infusion of propofol.[21–23] Previous experiments under the same conditions as those used in the current study have shown bolus administration of propofol 5 mg kg^{-1} to cause a rapid increase in the latency of the cortical surface mass evoked response.[10] This increase in latency became significantly different from the control value for latency within 50 s of the bolus and lasted 15 min after the administration of propofol. Propofol was thus clearly indicated as an agent with which to attempt computer-controlled regulation of the depth of anaesthesia in the rat.

Spontaneous fluctuations in depth of anaesthesia

Intentional changes in anaesthetic dosage, or in stimulation of the animal, cause well-characterized alterations in the latency of the evoked response, which have been described elsewhere.[14] In addition, however, for reasons which remain obscure, indices of the depth of anaesthesia, including evoked responses (both somatosensory and auditory), the electrocorticogram, respiration, heart rate and blood pressure, exhibit apparently spontaneous fluctuations.[14] These fluctuations are short-lived and vary about a relatively constant mean value. In order to avoid unnecessarily frequent changes in the control signals delivered to the infusion pump, data for latency change were smoothed using a low-pass digital filter which had a time constant of 24 s. Pilot experiments showed that this value was sufficient to damp short-lived fluctuations in the latency record without introducing a lag in controller responsiveness so great as to render the controller unable to compensate adequately for changes in the mean onset latency.

Automatic control of depth of anaesthesia

The results of this series of experiments show that it is possible to measure components of the somatosensory average evoked response in real time and to use this data as an index for the closed-loop control of delivery of an anaesthetic drug. Furthermore, the data suggest that it may be possible to regulate changes in the average evoked response, and thus in the depth of anaesthesia, on a moment-by-moment basis. Such a system would have the clear advantages of minimizing the subject's exposure to anaesthetic drugs, thus improving safety and cost-effectiveness while ensuring the delivery of appropriate quantities of these agents. The applicability of this system to the induction and maintenance of anaesthesia in initially conscious subjects could be demonstrated, subject to the necessary legal authority, by two series of fairly straightforward experiments. In the first series, animals could be anaesthetized and undergo surgery, as described above, using halothane (or some other readily reversible agent). With the control system activated, the halothane could be gradually withdrawn and, while concurrently monitoring physiological indices of arousal such as heart rate, blood pressure and electroencephalogram, the ability of the controller to maintain an appropriate depth of anaesthesia could be determined. In a second series of possible experiments, animals could be implanted chronically with intravenous cannulae and cortical surface electrodes (as described by Angel and Gratton).[20] After a period of postoperative recovery, the animals could be connected to the controller, which would be instructed to induce and maintain anaesthesia. We have undertaken significant refinement of our system of closed-loop control, which is described below. We suggest that tests of closed-loop control using somatosensory evoked potentials in conscious animals should be delayed until these refined systems of automation have been validated.

The mean rate of administration of propofol that was determined by the controller fell within the middle of the range of values which are reported in the literature for intravenous administration in rats. In the two animals shown in Fig. 3, the controller delivered a mean infusion rate of 32 and 27.6 mg kg^{-1} h^{-1}, respectively. These values are somewhat higher than the 14 mg kg^{-1} h^{-1} reported to be required for laparotomy in unpremedicated rats,[24] but are somewhat lower than the 40 mg kg^{-1} h^{-1} that Yang *et al* [25] found was necessary to achieve a plasma concentration of 1.7 μg ml^{-1}, which they associated with loss of the tail-flick reflex and profound electroencephalographic changes. The reason for this wide variation is unclear, but may result from such factors as differences in animal susceptibility, differences in handling and differences in stimulation paradigms. It is likely that it was necessary for propofol to reach a minimum brain concentration in our animals in order to cause changes in the latency of the evoked response. This concentration, and its dependence on the infusion rate, is unlikely to have been affected by concurrent anaesthesia with urethane and we were not surprised, therefore, to find that values for mean infusion rate fell within the mid-range of values reported in the literature.

Although this system was developed using experimental animals, we argue that the technique has relevance for the development of schemes for the control of anaesthesia in humans. Human somatosensory evoked potentials have been shown, like those in our animals, to undergo an increase in latency and a decrease in amplitude with progressively increasing concentrations of most anaesthetics.[9 26] The signal-to-noise ratio in human evoked response data is almost an order of magnitude poorer than that in animal studies. This problem may be overcome, however, using an appropriate, selective filtering scheme, such as that already incorporated in the latency change estimator.[27] It is thus conceivable that human somatosensory evoked potentials could be analysed in real time for use in a system of closed-loop control of drug delivery.

The system which we have described has the important limitation that it responds to changes in the latency of the evoked response. Thus, there is an inevitable time lag in response to changes in the biological signal which we have taken as an index of neurological arousal. The problem of lag is further compounded by the need, which we have described, to smooth the data so as to reduce the effect of biologically unavoidable spontaneous fluctuations in the evoked response. The effect of smoothing, which is essentially an autoregressive process, is thus to add further delay between the time of occurrence of a biological change and the onset of the system's response. The simplest means by which to minimize performance deterioration owing to time lag is to choose a short sampling period. A rule of thumb in choosing an adequate sampling period is to select a period with one-twelfth to one-quarter of the rise time of the response. In rats, the rise time of the response to propofol administration is approximately 50 s;[10] this indicates a range of sampling periods of 4–12 s. It is for this reason that we delivered stimuli at the rate of five per second, and hence achieved a sampling period of 6 s, so as to reduce, as far as possible, the time taken to acquire each measure of the average latency of response. A further stratagem for addressing this problem is to choose a set-point which is somewhat higher than that which is desired. This ensures that, at all times, the index of responsiveness remains safely above the set-point. This solution is less elegant, however, as it undermines one of the principal advantages of the closed-loop control system: that of minimizing the subject's exposure to anaesthetic.

The integral action of PI control is to eliminate steady-state error if the control parameters are selected appropriately. Selection of appropriate parameter values requires detailed model analysis and is only practicable in systems with consistent dynamics. It is unlikely, therefore, to be of use in living systems which have inherently varying dynamics. The difficulty associated with inappropriate control parameters is clearly reflected in Fig. 5, which shows a significant steady-state error during the automatic control period.

The problems of fluctuating response and steady-state error, which are caused by time lag and inappropriate parameter selection, has led us to combine the system of PI control, which we describe here, with a system of adaptive predictive control. We are currently working on such a system in which the controller 'learns' the susceptibility and the responsiveness of each animal to propofol. The controller can thus make changes to the infusion rate in anticipation of the resulting biological changes. Thus, the problem of lag in controller responsiveness will be addressed and the delivery of propofol will be even more finely tuned to the requirements of the individual.

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Effects of sevoflurane on hypoxic pulmonary vasoconstriction in anaesthetized piglets

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In vitro, halogenated agents reduce the pulmonary vasoconstrictor response to alveolar hypoxia in isolated perfused lungs. However, studies in intact animals have been less convincing. The aim of the present study was to assess the effect of sevoflurane on hypoxic pulmonary vasoconstriction (HPV) in anaesthetized piglets using the pressure/cardiac index relationship (*P*/*Q*).Ten large white piglets were anaesthetized and mechanically ventilated, alternately in hyperoxia ($F\text{I}_{O_2}$=0.4) and hypoxia ($F\text{I}_{O_2}$=0.12). Multipoint plots of pulmonary arterial pressure (PAP) or differences between PAP and left atrial pressure (LAP) against *Q* were generated by gradual inflation of a balloon introduced into the inferior vena cava. *P*/*Q* relationships were established in hyperoxia and hypoxia at baseline, and then with sevoflurane. In hypoxia, pressure gradients (PAP – LAP) increased at every level of *Q*, thus demonstrating active pulmonary vasoconstriction. Sevoflurane at 1 MAC did not affect these *P*/*Q* relationships in hyperoxia or hypoxia as compared with baseline. Sevoflurane at a clinically relevant concentration (1 MAC) has no significant effect on HPV in anaesthetized piglets.

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Pulmonary vasoconstriction in response to acute hypoxia helps to maintain arterial oxygen tension.[1] Impairment of this mechanism by inhalational anaesthetic agents has been implicated in hypoxemia during anaesthesia.[2] However, this conclusion is controversial since *in vitro* studies showing inhibition by halothane, enflurane, isoflurane and desflurane[3 4] have not been consistently confirmed by *in vivo* experiments in intact animals.[6–8]

Sevoflurane is a recently introduced inhalational anaesthetic. Its effects on hypoxic pulmonary vasoconstriction (HPV) have been the focus of a few studies. *In vitro* experiments using constant-flow perfused rabbit lung[5] confirmed concentration-dependent inhibition of vasoconstriction by sevoflurane. The only available study that we know of in intact chronically instrumented animals showed that sevoflurane did not inhibit hypoxic pulmonary vasoconstriction.[7]

The present study was designed to assess the effect of sevoflurane at the clinically relevant concentration of 1 MAC on HPV in intact anaesthetized piglets. Piglets were chosen as the study model because of their strong pulmonary vasoconstriction response to hypoxia.[9] Pulmonary haemodynamics were evaluated by multipoint *P*/*Q* plots, which provide a quantitative measure of the relationship between pulmonary vascular pressure (*P*) and cardiac index (*Q*).[10] Previous experiments have demonstrated that these plots are linear in intact anaesthetized piglets.[11]

Materials and methods

The study design was reviewed and approved by the animal ethics committee of the La Timone Medical School in Marseille. All procedures were compliant with the *Guiding Principles in the Care and Use of Animals of the American Physiological Society.*

Animal preparation

After a 12 h fasting period with free access to water, 10 large white piglets (22–31 kg, mean 25 kg) were premedicated

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with ketamine (20 mg kg^{-1} i.m.), midazolam (0.1 mg kg^{-1} i.m.) and atropine (0.25 mg i.m.) and placed in the supine position. Anaesthesia was induced with midazolam 0.1 mg kg^{-1} i.v., fentanyl 2 μg kg^{-1} i.v. and maintained with intravenous infusions of fentanyl 20 μg kg^{-1} h^{-1} and midazolam 0.1 mg kg^{-1} h^{-1}. Muscle paralysis was achieved with vecuronium bromide 1 mg kg^{-1} i.v. and maintained with an infusion of vecuronium bromide 2 mg kg^{-1} h^{-1} after tracheostomy had been performed. Lungs were mechanically ventilated via a no. 6 cuffed tracheostomy tube (Tracheosoft Lanz 101-70 i.d. 6.0; Malindkrodt Medical, Athlone, Ireland) with a servo ventilator B 900 (Siemens, Elema, Sweden) initially set to deliver a $F\mathrm{I}_{\mathrm{O}_2}$ of 0.4, a tidal volume of approximately 12–15 ml kg^{-1} and a respiratory rate adjusted to maintain an arterial Pa_{CO_2} between 4.7 and 5.3 kPa. No positive end-expiratory pressure was used. Sevoflurane was administered through a vaporizer adapted to the ventilator. Inspired and expired fractions of oxygen, carbon dioxide and sevoflurane were measured using an Ultima II infrared spectrophotometer (Datex, Helsinki, Finland).

Throughout the experiment, 0.9% sodium chloride was infused in the left internal jugular vein at 4 ml kg^{-1} h^{-1}. Temperature was maintained at 38–39°C using an electrical heating pad. Metabolic acidosis, when present, was corrected by slow infusion of triaminolacetate (THAM; Roger Bellon Laboratories, Neuilly-sur-Seine, France).

A thermistor-tipped Swan–Ganz catheter (93A-131-7F; Edwards Laboratories, Santa Anna, CA, USA) was inserted in the right internal jugular vein and positioned with reference to right arterial pressure (RAP), mean pulmonary arterial pressure (PAP) and mean capillary wedge pressure (PCWP). It was used to measure central core temperature and perform mixed venous blood sampling. A polyethylene catheter was placed in the abdominal aorta via the right femoral artery for systemic arterial pressure (SAP) measurements and arterial blood sampling. A balloon catheter (Redigard, 9F 40 ml; St Jude Medical Inc., Chelmsford, MA, USA) was placed in the inferior vena cava through a right femoral venotomy. Inflation of this balloon produced a gradual decrease in cardiac output by reducing venous return. All catheters were inserted through peripheral cut-down.

A left thoracotomy was performed to place a polyethylene catheter (Liddle LAP 17 G 50.6 cm; Research Medical Inc., Salt Lake City, UT, USA) via the atrial appendage into the left atrium to monitor left atrial pressure (LAP). The thoracotomy was hermetically closed and a tube (Argyle 24) was inserted into the pleural space and connected first to a vacuum pump and then to a water seal as soon as vacuum was achieved. Thrombus formation along the catheters was prevented by giving sodium heparin 100 IU $\mathrm{kg}.^{-1}$ i.v. just before insertion and 100 IU kg^{-1} h^{-1} continuously.

Measurements

Pulmonary, cardiac and systemic pressures were measured using disposable transducers (pressure monitoring kit; Baxter SA, Maurepas, France) connected to a multichannel monitor (Merlin; Hewlett-Packard Inc., Palo Alto, CA, USA). Zero reference was located at midchest, and readings were taken at the end of expiration. Heart rate was continuously recorded by three electrocardiographic leads connected to the same monitor. Cardiac output was rapidly measured at the end of expiration by the thermodilution technique using injections of 5 ml of 0.9% sodium chloride at 0°C. Results were analysed by a computer. Values correspond to means of at least three measurements after elimination of readings 10% higher or lower than the previous value. Haemodynamic data were sampled every 20 s, digitized and stored on the hard disc of a personal IBM PC/AT (Hewlett Packard Vectra 386 DX 33 with Hewlett Packard software). Arterial and mixed venous pH, $P\mathrm{CO}_2$ and $P\mathrm{O}_2$ were measured immediately after drawing the samples using an automated analyser (ABL 500; Radiometer, Copenhagen, Denmark), all blood gas values were corrected according to central temperature. Body surface area (m^2) was calculated as $0.112 \times \mathrm{weight}^{2/3}$ (kg).

Protocol

After ensuring steady-state conditions for 10 min at an $F\mathrm{I}_{\mathrm{O}_2}$ of 0.4 (stable SAP, PAP, LAP, Q, end-tidal carbon dioxide and heart rate), a first four-point P/Q plot was generated in 20 min: the first point corresponding to basal cardiac output followed by one point for each incremental inflation of the vena cava balloon (three points). Each P/Q point construction took 5 min. A similar plot was constructed at an $F\mathrm{I}_{\mathrm{O}_2}$ of 0.12 for 30 min when Pa_{O_2} reached 5.3–6.7 kPa. Previously reported stimulus–response curves for HPV in intact anaesthetized ventilated piglets have shown that the whole-lung hypoxic pressor response is undetectable if $F\mathrm{I}_{\mathrm{O}_2}$ is >0.3 and maximal when $F\mathrm{I}_{\mathrm{O}_2}$ is 0.12.[11] Similar plots were generated at $F\mathrm{I}_{\mathrm{O}_2}$ 0.4 and at $F\mathrm{I}_{\mathrm{O}_2}$ 0.12 with 2.6% end-tidal sevoflurane. Finally, return to baseline, defined as end-tidal sevoflurane concentration around zero, was tested in hyperoxia and hypoxia. Haemodynamic parameters (SAP, LAP, RAP, PCWP, PAP, heart rate) and arterial and mixed venous blood gases were measured at each phase of the study and Q level. Repeated exposure to hypoxia was performed to make sure that the magnitude of HPV was constant throughout this experiment.

Statistical analysis

Individual PAP/Q, (PAP – LAP)/Q and (PAP – PCWP)/Q plots appeared to be linear, so a linear regression analysis (least squares method) was used to compute slopes. Q was considered as the independent variable and P as the dependent variable. To obtain composite P/Q plots, pressures interpolated from the regression analysis from indi-

Table 1 Effects of sevoflurane on haemodynamic data. Values are means (SD) (n=10 piglets). Abbreviations: H and L, highest and lowest cardiac index (Q), respectively, SAP, mean systemic arterial pressure, PAP, mean pulmonary artery pressure; PCWP, mean capillary wedge pressure, LAP and RAP, mean left and right atrial pressure, respectively. $Significant difference ($P$<0.05) compared with base line at the same $F\text{I}_{\text{O}_2}$, #significant difference (P<0.05) compared with the corresponding stage in hyperoxic animals, *significant difference (P<0.05) between highest and lowest Q at the same stage

	Q	**Hyperoxia ($F\text{I}_{\text{O}_2}$=0.4)**			**Hypoxia ($F\text{I}_{\text{O}_2}$=0.12)**		
		Baseline	**Sevoflurane MAC 1**	**Return**	**Baseline**	**Sevoflurane MAC 1**	**Return**
Q (litre min^{-1} m^{-2})	H	2.0 (0.2)	2.0 (0.2)	2.3 (0.1)	2.2 (0.2)	1.8 (0.2)	2.3 (0.2)
	L	1.1 (0.1)*	1.1 (0.1)*	1.0 (0.1)*	1.1 (0.1)*	1.1 (0.2)*	0.9 (0.1)*
Heart rate (beats min^{-1})	H	120 (7)	159 (8)$	143 (10)	137 (8)	150 (7)	151 (8)
	L	163 (6)*	166 (7)*	190 (9)*$	184 (7)*#	166 (12)*	198 (11)*
SAP (mm Hg)	H	128 (6)	94 (5)$	121 (3)	128 (9)	73 (4)$#	114 (3)
	L	95 (11)*	56 (4)*$	63 (5)*$	85 (9)*	50 (5)*$	58 (4)*
PAP (mm Hg)	H	21 (1)	22 (1)	25 (2)	38 (2)#	34 (2)#	45 (2)#
	L	15 (1)*	16 (1)*	16 (2)*	23 (2)*#	20 (1)*	21 (3)*
LAP (mm Hg)	H	9 (1)	9 (1)	8 (1)	9 (1)	10 (1)	11 (1)
	L	6 (1)*	6 (1)*	7 (1)*	7 (1)*	6 (1)*	8 (2)*
RAP (mm Hg)	H	8 (1)	8 (1)	8 (1)	7 (1)	8 (1)	8 (1)
	L	5 (1)	6 (1)	7 (2)	5 (1)	6 (1)	6 (2)
PCWP (mm Hg)	H	8 (2)	9 (1)	9 (1)	9 (1)	10 (1)	12 (1)
	L	5 (1)*	7 (1)*	7 (1)*	7 (1)*	7 (1)*	8 (1)*

vidual piglets were averaged at 0.5 litre min^{-1} m^{-2} intervals of Q from 0.5 to 2.5 litre min^{-1} m^{-2}. Blood gas and haemodynamic data were analysed by analysis of variance for serial measurements. When the significance of a factor was P<0.05, a Bonferroni *post hoc* test was performed to compare specific situations. Slopes of composite P/Q plots were compared by Student's t-test. Data are expressed as mean (SD). All analyses were performed with Statview 4 software (Abacus concept) on a Macintosh Power PC 6200/75 personal computer.

Results

Induced variations of cardiac index

Stepwise inflation of the balloon catheter in the inferior vena cava induced variations in Q. Mean values ranged from 1 to 2.3 litre min^{-1} m^{-2} (Table 1). The PAP/Q, (PAP–LAP)/Q and (PAP–PCWP)/Q relationships were linear in all experimental conditions (Table 2). Blood gases mainly changed by a decrease in mixed venous $P\text{O}_2$ at the lowest Q (Table 3).

Baseline values in hyperoxia and hypoxia

Hypoxia markedly decreased arterial and mixed venous $P\text{O}_2$ with no change in pH or Pa_{CO_2} (Table 3). SAP, LAP, RAP and PCWP were the same in hypoxic and hyperoxic conditions. Over the full range of Q studied, hypoxia increased PAP (P<0.01) (Figure 1), while it significantly increased heart rate only for the lowest Q. The main sign of hypoxic pressor response was a significant increase in the slopes of PAP/Q, (PAP–LAP)/Q and (PAP–PCWP)/Q relationships.

Table 2 Slopes and correlation coefficients (r^2) corresponding to composite P/Q plots made in hyperoxia ($F\text{I}_{\text{O}_2}$=0.4) and hypoxia ($F\text{I}_{\text{O}_2}$,=0.12) at baseline, with sevoflurane, and after return to baseline. Values are means (SD) (n=10 piglets). *Significant difference (P<0.01) for comparison between slope at $F\text{I}_{\text{O}_2}$ 0.4 and that at $F\text{I}_{\text{O}_2}$ 0.12 in the same step. #Significant difference (P<0.05) for comparison of slopes at different steps at the same $F\text{I}_{\text{O}_2}$

	$F\text{I}_{\text{O}_2}$	**PAP**	**PAP–LAP**	**PAP–PCWP**
Baseline				
Slope (mm Hg litre^{-1} min m^2)	0.4	6.9 (0.4)	3.8 (0.6)	4.1 (0.5)
	0.1	13.8 (1.0)*	12.1 (1.2)*	11.9 (0.5)*
r^2	0.4	0.92	0.83	0.82
	0.1	0.94	0.93	0.94
Sevoflurane				
Slope (mm Hg litre^{-1} min m^2)	0.4	6.5 (0.9)	3.8 (0.6)	4.2 (0.6)
	0.1	16.6 (1.5)*	12.2 (1.4)*	13.1 (1.3)*
r^2	0.4	0.88	0.80	0.83
	0.1	0.87	0.81	0.84
Return				
Slope (mm Hg litre^{-1} min m^2)	0.4	7.0 (1.2)	5.4 (1.2)	5.3 (1.3)
	0.1	15.9 (1.1)*	13.5 (1.6)*	13.4 (1.6)*
r^2	0.4	0.92	0.87	0.82
	0.1	0.92	0.93	0.88

Sevoflurane in hyperoxia

Sevoflurane (2.6% end-tidal) significantly increased heart rate and significantly reduced SAP compared with baseline (P<0.05), whereas PAP, LAP, RAP, PCWP were unchanged. At lowest Q, SAP was significantly lower than at baseline (P<0.05).

Sevoflurane in hypoxia

In hypoxia, administration of 2.6% end-tidal sevoflurane increased heart rate at highest Q and reduced SAP compared

Table 3 Effects of sevoflurane on blood gases. Values are means (SD) (n=10 piglets) Abbreviations H and L, highest and lowest values of Q, respectively *Significant difference (P<0.05) between highest and lowest Q at the same stage; #significant difference (P<0.05) compared with the corresponding stage in hyperoxic animals

	Q	**Hyperoxia ($F\text{I}_{\text{O}_2}$=0.4)**			**Hypoxia ($F\text{I}_{\text{O}_2}$=0.12)**		
		Baseline	**Sevoflurane MAC 1**	**Return**	**Baseline**	**Sevoflurane MAC 1**	**Return**
pH$_a$	H	7.43 (0.01)	7.42 (0.01)	7.39 (0.02)	7.43 (0.01)	7.44 (0.01)	7.39 (0.01)
	L	7.42 (0.01)	7.42 (0.01)	7.39 (0.01)	7.39 (0.02)*	7.44 (0.02)*	7.35 (0.02)*
Pa_{O_2} (kPa)	H	19.5 (1.1)	18.4 (1.7)	19.5 (1.5)	5.5 (0.3)#	5.9 (0.5)#	5.5 (0.3)#
	L	20.1 (1.1)	20.8 (1.3)	20.3 (1.7)	5.7 (0.3)*#	6.3 (0.3)*#	6.5 (0.3)*#
Pa_{CO_2} (kPa)	H	5.7 (0.1)	5.3 (0.1)	5.6 (0.1)	5.5 (0.1)	5.2 (0.1)	5.9 (0.1)
	L	5.3 (0.1)	5.3 (0.1)	5.6 (0.1)	5.3 (0.1)*	4.9 (0.1)*#	5.3 (0.3)*
$P\text{v}_{\text{O}_2}$ (kPa)	H	6.4 (0.4)*	5.6 (0.3)	6.4 (0.3)	3.5 (0.3)#	3.6 (0.1)#	3.3 (0.3)#
	L	4.5 (0.3)	4.7 (0.3)*	4.9 (0.7)*	2.8 (0.1)*#	3.2 (0.1)*#	2.8 (0.1)*#

with baseline. PAP, LAP and PCWP were unchanged (Table 1). No inhibitory effect on hypoxic pressor response was observed (Figure 1). Sevoflurane had no effect on Pa_{O_2}, pH$_a$, $P\text{v}_{\text{O}_2}$, Pa_{CO_2} at highest Q. At the lowest Q, $P\text{v}_{\text{O}_2}$ was slightly lower than at the highest Q.

Stability and reproducibility of HPV–baseline return

At constant Q, three sequences of alternating 30 min periods at a $F\text{I}_{\text{O}_2}$ of 0.4 and 0.12, there was essentially no change in blood gases (Table 3) or in haemodynamics in the successive periods at the same $F\text{I}_{\text{O}_2}$ (Table 1). No change in PAP occurred at the same $F\text{I}_{\text{O}_2}$ The hypoxia-induced increase in PAP recurred during the third hypoxic episode (Table 1).

Discussion

The present study was designed to assess the effect of sevoflurane on HPV in intact piglets. *P*/*Q* plots were generated in 10 piglets anaesthetized with midazolam and fentanyl, and mechanically ventilated. Sevoflurane at a clinically relevant dose induced marked systemic vasodilation (decrease in SAP with an unchanged Q), but HPV was unaffected by this anaesthetic. The end-tidal concentration of sevoflurane studied is equivalent to 1 MAC in pigs.[12] Higher concentrations are required to induce a relevant effect on HPV in the isolated lung.[5] This concentration was chosen because it is equivalent to that used in clinical settings when in combination with opiates.

One *in vitro* study has demonstrated that sevoflurane inhibits the HPV response in a dose-related manner, in constant flow-perfused rabbit lung.[5] To our knowledge, only one study has assessed the effects of sevoflurane on HPV in chronically instrumented and unsedated animals,[7] and no previous experiment has been performed in anaesthetized animals.

The *P*/*Q* plots in our piglets were linear under all experimental conditions, in keeping with previous studies in intact anaesthetized[5] or unsedated animals.[10]

The technique we used to assess pharmacological and physiological variations in pulmonary vasomotor tone involved generation of multipoint *P*/*Q* plots. This technique was developed by Lodato, Michael and Murray in conscious dogs, at two different inspired oxygen concentrations.[10] The inferior vena cava occlusion technique, involving incremental inflation of a balloon catheter, produced a titratable decrease in Q. *P*/*Q* plots were then generated. This *P*/*Q* relationship allows vasoactive effects on the pulmonary circulation to be distinguished from passive mechanical effects. This technique is more relevant than use of calculated pulmonary vascular resistance, which does not take in consideration how this resistance varies with Q. However, it has a number of limitations, including systemic hypotension, changes in blood gases and changes in zonal conditions of the lung. This technique has already been used in mammals to test anaesthetic effects,[6 10] and physiological or metabolic manipulations on HPV.[11 14]

HPV varies widely between individuals and species.[13] Twelve-week-old piglets were selected for our study since they show a stronger pressor response to hypoxia than most other mammals.[9 13]

Some factors may alter pulmonary vascular pressor response to hypoxia in animals: First, increasing LAP can reduce HPV in anaesthetized animals. This suggests that the whole pulmonary vasculature does not behave as a Starling resistor in hyperoxia or hypoxia.[14] In our piglets, LAP did not change throughout study, and so could not have modified pulmonary vascular response to hypoxia.

Second, alternating hyperoxia and hypoxia and repetition of hypoxic episodes enhance HPV.[15] In our study, PAP/Q plots increased between baseline and baseline return in hyperoxia and in hypoxia, but this variation was not significant and probably did not influence the mechanism of HPV.

Third, although pressor response is usually dependent on Pa_{O_2}, major changes in mixed venous $P\text{v}_{\text{O}_2}$ can modify the magnitude of HPV.[16] In our study, hypoxia and low Q led to a marked decrease in $P\text{v}_{\text{O}_2}$ in both cases. This decrease could have enhanced HPV.

Fourth, pressor response can be altered by changes in arterial pH and Pa_{CO_2}.[17] In anaesthetized dogs, marked alkalosis induced by artificial hyperventilation during hypoxia reduces PAP.[17] This was unlikely to have occurred

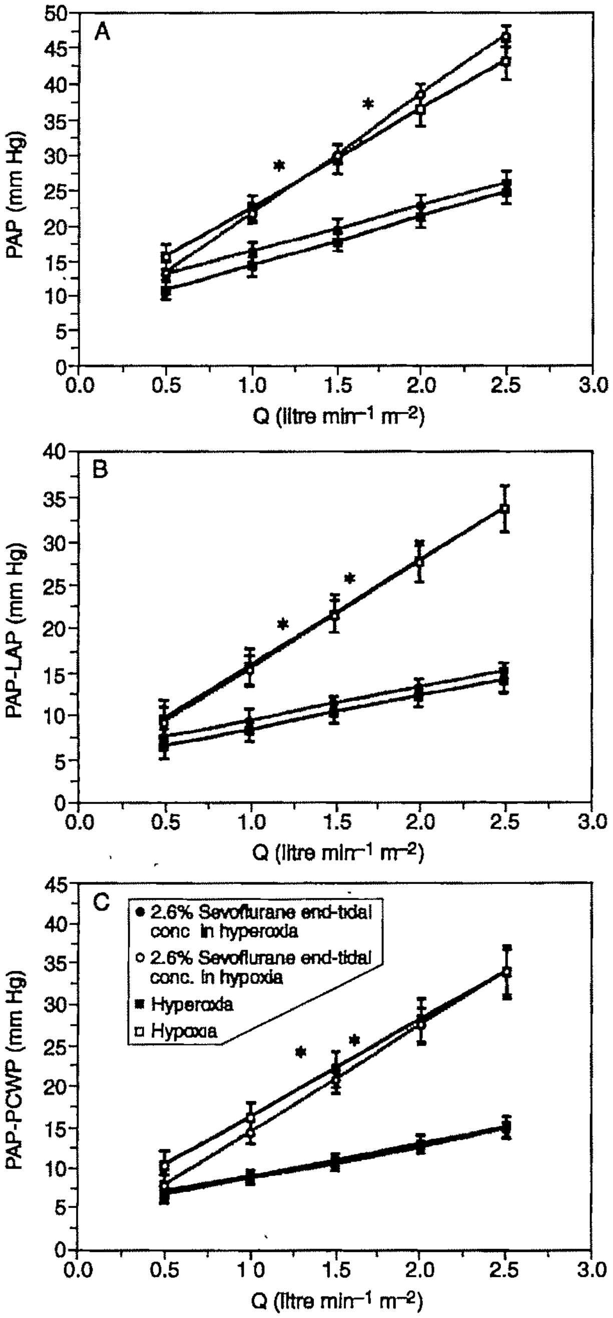

Fig 1 Extrapolated plots of (a) PAP, (b) PAP–LAP and (c) PAP–PCWP against cardiac index (*Q*) at baseline, in hyperoxia (■) and hypoxia (□), and with 2.6% sevoflurane end-tidal concentration in hyperoxia (●) and hypoxia (○). *$P<0.05$ for comparison of slopes between hyperoxia and hypoxia. Values are means±SEM, $n=10$ piglets.

in our study since arterial pH and Pa_{CO_2} were kept constant at all levels of *Q*.

Finally, reduction of *Q*, as was performed in our experiment, activates the arterial baroreceptor reflex. Carotid sinus baroreceptor reflex directly controls the entire systemic and pulmonary arterial pressure–flow relationships in anaesthetized dogs.[18] In intact conscious dogs, circulatory hypotension resulted in active pulmonary vasoconstriction, primarily mediated by sympathetic α_1 adrenoreceptor activation.[19] In our study, at baseline, activation of baroreceptor reflex by lowering *Q* was not effective, as suggested by the lower PAP at lowest *Q* in both hyperoxia and hypoxia.

As in previous data with other inhalational anaesthetics in intact mammals, sevoflurane induced only systemic vasodilation and had no significant effect on HPV, when it was used at 1 MAC. Investigations assessing the effects of halogenated agents on HPV have produced different results, depending on the experimental model. Studies on isolated perfused lungs showed that inhaled agents inhibited HPV.[3–5] Conversely, experiments with intact mammals showed either inhibition[20] or no significant effect.[7 21]

Many factors could account for the conflicting results of *in vivo* studies.

Associated intravenous anaesthetics. This experiment, including a thoracotomy, the placement of a balloon catheter into the inferior vena cava and several hours of immobilization, required general anaesthesia and mechanical ventilation. These anaesthetic conditions were close to those used in clinical settings, where sevoflurane is administered with fentanyl.[22] Neither fentanyl nor midazolam has any recognized effect on pulmonary vascular tone.[23] Pentobarbital sodium was not used in this study because a previous report showed that it might have a slight inhibitory effect on HPV in intact piglets.[11] Moreover, in isolated perfused sheep lungs, pentobarbital sodium decreased HPV by 14–28% when administered at concentrations used in anaesthesia.[24]

Mechanical ventilation. Intermittent positive pressure ventilation can affect the pulmonary circulation in various ways, such as by directly compressing alveolar vessels and by increasing lung volume.[25] This could explain the differences observed between mechanically ventilated and unsedated intact animals. In our experiment, pulmonary vascular pressures were measured at the end of expiration when pleural pressure was presumably lowest. However, effects of mechanical ventilation on pulmonary vascular tone cannot be ruled out.

Site of action of hypoxia. The site of action of hypoxia may vary among species. In dogs, HPV is thought to occur mainly in pulmonary arteries,[26] whereas capillaries may be the major site of vasoconstriction in pigs.[27]

Action of the sympathetic nervous system. In anaesthetized dogs, chemical sympathectomy or chemodenervation increased PAP at all levels of *Q* studied both in hypoxia and in hyperoxia.[28] The effect of the sympathetic nervous system in hyperoxic and hypoxic healthy mammal lungs seems to reduce pulmonary vascular tone. In our study, administration of sevoflurane in hyperoxia probably induced a sympathetic activation as judged by the significant increase of heart rate compared with baseline. This activation was less evident in hypoxia, in which there was a non-significant increase in heart rate. In these conditions, sevoflurane could have partially altered the baroreflex. The effect of sevoflurane on HPV in the intact animal is therefore less evident than in the isolated lung, when the autonomic nervous system is not effective. This could explain the discrepancies between *in vitro* and *in vivo* studies on sevoflurane.

In summary, we assessed the effects of sevoflurane on HPV at 1 MAC, in intact anaesthetized mechanically ventilated piglets. This was allowed by generation of pulmonary vascular *P/Q* relationships which were linear in hyperoxia and hypoxia and with sevoflurane. Hypoxia resulted in a significant increase in pressure gradients (PAP–LAP) and (PAP–PCWP) because of active pulmonary vasoconstriction. Sevoflurane did not appear to influence hypoxic pulmonary vasoconstriction. These findings are different from those obtained in *in vitro* experiments, but in agreement with those from a previous *in vivo* study.[7] Therefore this halogenated agent seems not to inhibit HPV in intact animals, whether in the conscious or anaesthetized state.

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REVIEW ARTICLE

Peri-operative management of patients with coagulation disorders

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Coagulation problems may be broadly divided into disorders of haemostasis and disorders of thrombosis, although there is a small intermediate group which involves both disorders. The special requirements of such patients in the peri-operative period will be discussed in the setting of the underlying condition.

Inherited disorders of haemostasis

A broad classification of the inherited disorders of haemoplasm is set out in Table 1.

The haemophilias

The haemophilias are characterized by a deficiency of coagulant factor which leads to increased bleeding at surgery and in the postoperative period. In the absence of platelet dysfunction, the bleeding time is normal.

Haemophilia A and haemophilia B

Haemophilia A, the most common of the haemophilias, is associated with deficiency of factor VIII coagulant protein. Haemophilia B (Christmas disease) is caused by deficiency of factor IX coagulant protein. Both these conditions have sex-linked recessive inheritance, affected males being born to carrier females, although up to 50% of cases appear *de novo* as a result of new mutations. The clinical severity of bleeding relates directly to the degree of deficiency. Spontaneous bleeding, classically haemarthroses, occur in severe cases (<2% coagulant factor VIII) while the moderately deficient (2–10% coagulant factor VIII) and those mildly affected (>10% coagulant factor VIII) may be expected to bleed excessively only after trauma or surgery. Some of the carrier females have significantly reduced coagulation factors and may behave clinically as mild cases themselves. This is particularly important in obstetric practice and in the peri-operative period, when specific replacement therapy may be required.

Over the last 50 yr, there has been progressive refinement in the provision of specific coagulant factor replacement therapy from fresh whole blood to the plasma-free recombinant products which have become available in the last 10 yr. In the intervening period, coagulation factor concentrates were obtained by fractionation from human plasma pooled from several thousand donations. Before the introduction of viral inactivation in 1985, the vast majority of patients treated with concentrate, which was thus derived from pooled plasma, contracted transfusion-transmitted hepatitis C (HCV) and half of those in the UK with severe haemophilia also acquired the human immunodeficiency virus (HIV).

In view of this history, therapeutic strategies to replace coagulation factors are also designed to minimize exposure to plasma components wherever possible.[47] Recommended therapeutic products are described in Table 2. For major surgery, a target concentration of 100% factor VIII is set to be maintained for the first 5–7 postoperative days, whereas minor procedures may be adequately covered by concentrations of 50% after the first day. Doses of factor VIII required to meet these targets are listed in Table 3. Many patients with moderate or mild haemophilia A produce a 2- to 4-fold increase in factor VIII in response to 1-deamino-8-D-arginine vasopressin (DDAVP), which will be adequate to cover minor surgery. Where higher concentrations are required, recombinant coagulant factor concentrate is the recommended replacement for all new patients and for children under 16 yr with haemophilia A and haemophilia B. For those over 16 yr, already established on treatment, high-purity coagulant factor replacement may be used. Since 1985, all such plasma products have been subjected to viral inactivation by heat treatment or a solvent detergent method

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Table 1 Inherited disorders of haemostasis

Disorder	Pathophysiology (deficiency or defect)	Inheritance	Incidence per million
Haemophilia A	Factor VIII	X-linked recessive	100
Haemophilia B (Christmas disease)	Factor IX	X linked recessive	20
Haemophilia C	Factor XI	Autosomal dominant or recessive	5% Ashkenazi Jews (others rare)
Von Willebrand's disease	Von Willebrand factor	Autosomal dominant or recessive	>100
Factor X deficiency	Factor X	Autosomal recessive	1
Factor V deficiency	Factor V	Autosomal recessive	1
Factor VII deficiency	Factor VII	Autosomal rececessive	1
Prothrombin deficiency	Factor II	Autosomal rececessive	1
Afibrinogenaemia	Factor I		1
Factor XIII deficiency	Factor XIII		1
Factor V plus VIII deficiency			1
Dysfibrinogenaemia	Factor I	Autosomal dominant	1

Table 2 Therapeutic materials for the treatment of haemophilia

Material	Factor VIII	Von Willebrand factor	Advantages	Disadvantages
DDAVP	–	–	No risk infection	Only effective in mild cases Tachyphylaxis
Intermediate-purity factor VIII concentrate	20–50 IU ml^{-1}	20–50 IU ml^{-1}		Non-factor VIII proteins present Plasma-derived
High-purity factor VIII concentrate	= 5000 IU mg^{-1} before addition of albumin carrier	–	Convenience	Plasma-derived Expensive
Recombinant factor VIII	= 5000 IU mg^{-1} before addition of albumin carrier	–	PureNo risk of infection	Very expensive Limited supply

to kill viruses with a lipid envelope (e.g. hepatitis B virus, HCV and HIV). More recently, an additional terminal filtration step has been introduced by some manufacturers to prevent the transmission of viruses which lack a lipid envelope, such as human parvovirus B19 and hepatitis A, by their products.

Haemophilia C (factor XI deficiency)

Factor XI deficiency[29] is sometimes know as haemophilia C, despite its different mode of inheritance and clinical features. It is an autosomal recessive condition, particularly common in Ashkenazi Jews. Homozygotes usually have factor XI concentrations less than 4% whereas heterozygotes have a wide range of concentrations (between 15 and 65%), but the bleeding diathesis may not correlate well with factor concentrations. Factor XI has a long half-life and replacement therapy may be required only infrequently after operation. A plasma-derived, virally inactivated factor XI concentrate is available for use but is recognized to be thrombogenic in some individuals. Where factor XI is used, the target concentration should not exceed 70% for this reason. Fresh-frozen plasma contains adequate amounts of factor XI[46], and now that this product is available in a virally inactivated form some clinicians prefer to use it to minimize thrombotic complications.

Table 3 Plasma levels of factor VIII to achieve haemostasis

Clinical indication	Plasma factor VIII target (IU dl^{-1})	Dose of factor VIII (IU kg^{-1})
Early haemarthrosis or muscle bleed	15–20	8–10
Minor trauma or more severe bleeding	30–50	15–25
Surgery, major trauma or head injury	80–120	40–60

Von Willebrand's disease

The basic defect in this condition is abnormal production of von Willebrand factor (vWF), a long protein monomer produced from the Weible Palade bodies of endothelial cells and from the alpha granules of platelets. vWF functions primarily in platelet adhesion to the subendothelial layers at high shear rates and, in addition, acts as a carrier molecule for factor VIII coagulant protein in the circulation. Hence, the clinical presentation is characterized by mucosal bleeding and easy bruising in association with a prolonged bleeding time in the majority of kindreds, where inheritance is autosomal dominant. It is the commonest of the inherited bleeding disorders, and it has been suggested that it might be present in as many as 20% of women with menorrhagia. Very rarely, the condition occurs in a severe form with autosomal recessive inheritance, very low concentrations of vWF and clinical features more like classical haemophilia, spontaneous haemarthroses occurring as well as mucosal bleeding.

Von Willebrand's disease is diagnosed[48] by measuring factor VIII coagulant protein (VIIIc), vWF antigen (vWFAg) and platelet activity as an estimate of binding to platelet glycoprotein with ristocetin as cofactor (vWRiCof), all of which will be reduced to 40% or less, giving rise to a prolonged bleeding time in the presence of a normal platelet count. These assays are, however, measuring labile factors which are influenced by stress and the results may therefore be variable and require repetition to confirm the diagnosis.

It is usually possible to avoid the use of blood components to control haemorrhage in the majority of cases of von Willebrand's disease. The antifibrinolytic agent tranexamic acid reduces minor bleeding, e.g. menorrhagia or epistaxis, and is prescribed in the postoperative period. DDAVP administered 90 min before operation at a dose of 0.3 $\mu g\ kg^{-1}$ may be expected to increase concentrations of vWFAg and factor VIII coagulant protein to normal (>100 $IU\ ml^{-1}$) in the majority who have a quantitative defect of vWFAg. Although further doses may be given postoperatively, the effect is maximal on first administration of DDAVP in any treatment episode as tachyphylaxis is well recognized. In a small proportion of cases, namely those with a qualitative defect of vWFAg or with the more severe autosomal recessive type, a plasma product will be required to supplement vWFAg and VIIIc together. Haemate P (Centeon) and 8Y (BPL) are two intermediate-purity factor VIII concentrates which fulfil these criteria and are licensed for use in the UK.

Inherited platelet disorders

These are uncommon conditions. Inherited thrombocytopenia of clinical significance will usually be diagnosed in childhood and platelet concentrates are required to support surgery. The better-defined thrombocytopathias (platelet function defects) are also very rare.

Glanzmann's disease

Glanzmann's thrombaesthenia is characterized by the absence of platelet glycoprotein II_b/III_a, which binds fibrinogen and is the site of the platelet-specific HPA 1a antigen. Platelet transfusion[35] in patients with Glanzmann's thrombaesthenia is therefore associated with the development of anti-HPA 1a antibodies, necessitating the selection of donors lacking this antigen. Sometimes, HLA selection may be required in addition.

Bernard–Soulier disease

This is associated with a defect of platelet binding to collagen, demonstrated by absent aggregation on exposure to ristocetin. Glycoprotein I_b/IX, which is the platelet-binding site for collagen, is not, however, associated with a platelet-specific antigen site, and patients may usually, therefore, be repeatedly transfused with platelet concentrate[35] without acquiring specific antibodies.

Platelet storage pool defects

Far more common, but with less well-defined causes, are the platelet storage pool defects, many of which are reversed by administration of DDAVP. Where this agent fails to correct a prolonged bleeding time, transfusion with platelet concentrate will be required to cover surgery. Since the introduction of universal leukodepletion of platelet concentrate in the UK in 1998, the incidence of febrile transfusion reactions and development of HLA antibodies has been significantly reduced.[8 34]

Acquired disorders of haemostasis

Consumptive coagulopathies

The consumptive coagulopathies are a spectrum of disorders characterized by inappropriate and widespread small vessel thrombosis, associated with generalized bleeding as a result of the consumption of coagulation factors and excessive fibrinolysis. Very often, a microangiopathic haemolytic anaemia ensues as red cells are damaged passing through blood vessels distorted by thrombosis. Although several distinct syndromes are described, the first line of management is to diagnose and treat the underlying cause.

Disseminated intravascular coagulation (DIC)

DIC is the most common consumptive coagulopathy, often with a prodromal thrombocytopenia giving way to hypofibrinogenaemia as a result of excessive fibrinolysis, the latter demonstrated by increased fibrin(ogen) degradation products and D-dimers. In the absence of sepsis or obstetric causes, extensive endothelial damage with collagen exposure may initiate the process. The main causes of DIC are listed in Table 4.

In this condition, there is rarely an underlying immune cause, and transfusion support should be guided by clinical signs and coagulation results to include platelet concentrate,[35] fresh frozen plasma,[46 52] cryoprecipitate (as a source of fibrinogen) and red cells. During 1999, component preparation was modified to ensure that all red cells, as well as platelet concentrate produced within the UK, are leukodepleted at source to minimize febrile reactions and HLA sensitization. A number of other agents have been advocated in certain specific situations.[38] Antithrombin III[12] concentrate may reverse the DIC process in septicaemia, with notable success in meningococcal infection. It has been suggested that protein C concentrate[42] may be equally effective in paediatric practice, but comparative data are difficult to evaluate in view of the extensive therapeutic support which is required to achieve a successful outcome in such patients. Where platelet activation is thought to be the

Table 4 Aetiology of disseminated intravascular coagulation

Condition	Examples
Infection	Septicaemia, e.g. meningococcaemia Viraemia Protozoa, e.g malaria
Malignancy	Metastatic carcinoma Haematological (especially acute promyelocytic leukaemia)
Obstetric disorders	Septic abortion Placental abruption Pre-eclampsia (pregnancy-induced hypertension) Amniotic fluid embolism Placenta praevia
Shock	Trauma Burns Heat stroke
Liver disease	Cirrhosis Acute hepatic necrosis
Transplantation	Tissue necrosis
Extracorporeal circulation	Cardiopulmonary by pass
Intravascular haemolysis	ABO incompatible blood transfusion Snakebite

Table 5 Classification of autoimmune thrombocytopenia

A Idiopathic (primary)
  A diagnosis of exclusion of secondary causes
B Secondary
  Drug-induced
    Drug-dependent
    Drug-independent
    Autoimmune systemic disorders
    Organ-specific, e.g. thyroid
    Haematological, e.g. Evans syndrome
    Generalized, e g. systemic lupus erythematosus
  Malignant disease
    Non-Hodgkin's lymphoma
    Chronic lymphocytic leukaemia
    Carcinoma
  Postinfective
    Childhood virus
  Immunodeficiency
    Post-transplant
    Chemotherapy, radiotherapy
    HIV

primary cause, prostacyclin has been tried. Aprotonin may be helpful where the original problem is thought to be fibrinolysis. The use of antifibrinolytic agents may, however, be complicated by the formation of permanent clot in undesirable sites such as small renal blood vessels.

The prescription of heparin is controversial,[13] with reports of benefit in amniotic fluid embolism,[23] but is a brave course to take in the haemorrhagic patient. In acute promyelocytic leukaemia, however, where disseminated intravascular coagulation is a frequent association, heparin and platelet support may be used to advantage to cover remission induction[1 22] and sometimes an antifibrinolytic agent may be helpful, depending on the coagulation profile.

Microangiopathic haemolytic anaemias

Less common are the microangiopathies, which are thought to be immune in origin and in which platelet transfusion is contraindicated.

Thrombotic thrombocytopenic purpura (TTP). In TTP, there is a predominantly neurological deficit caused by thrombosis in small cerebral vessels in association with fever and thrombocytopenia, and there is often evidence of an underlying immune disorder. Recently, it has been shown that there is an increase in very large molecular weight multimers of vWF as a result of the formation of an antibody to their cleaving metalloprotease.

Haemolytic uraemic syndrome (HUS). By contrast, HUS features renal dysfunction with thrombocytopenia, often after an infection, particularly with enteric pathogens which produce a verotoxin in children.

In both HUS and TTP, thrombocytopenia is the predominant haematological feature, in association with microangiopathic haemolysis. The treatment for both conditions is total plasma exchange ($1\frac{1}{2}$ volumes), replacing with cryoprecipitate supernatant[2 39] plasma, which is deficient in high molecular weight von Willebrand multimers. Platelet transfusion must be avoided.

The immune thrombocytopenias

The main causes of autoimmune thrombocytopenias are described in Table 5. Their prognosis and management varies according to their causative antibody and presentation.[15 16 25] An acute thrombocytopenia caused by IgM antibodies is the commonest form in childhood, commonly following a viral illness and usually recovering spontaneously with no need for therapeutic intervention.

Adults, by contrast, are more likely to acquire an IgG-mediated disorder which runs a chronic course and requires immunosuppressant therapy. Although some individuals remit on steroids, many relapse when treatment is stopped, and in this group splenectomy offers a 50% chance of cure. The platelet count may be improved in preparation for surgery using a course of i.v. immunoglobulins at a dose of 0.4 mg kg^{-1} daily for 5 days, a target platelet count of 80–100 × 10^9 litre^{-1} being considered adequate to secure haemostasis at operation. The introduction of laparoscopic technology to perform splenectomy has reduced the morbidity of the procedure significantly.[3]

The permanent risk of overwhelming postsplenectomy infection remains. Vaccination against pneumococcal pneumonia should be administered before operation in the form of Pneumovax and pneumococcal antibodies quantitated every 5–10 yr, with booster immunization as necessary. To obtain an optimal response, immunization should start 2–3 months before surgery. In addition, vaccination against *Haemophilus influenzae* B and the meningococcal strains A and C should be provided, with a recommendation for lifelong oral prophylaxis against encapsulated organisms with daily penicillin V or erythro-

Table 6 Causes of maternal thrombocytopenia in pregnancy

- Spurious
- 'Benign' gestational thrombocytopenia of pregnancy
- Autoimmune thrombocytopenia
  - Idiopathic
  - Drug-related
  - HIV–associated
- Pre-eclampsia; HELLP syndrome
- Disseminated intravascular coagulation (DIC)
- Haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenia purpura (TTP)
- Severe folate deficiency
- Others (rare)
  - Congenital, e.g. May–Hegglin, Bernard–Soulier
  - Hypersplenism
  - Coincidental marrow disease

mycin.[33] In view of the rebound thrombocytosis which usually occurs immediately after operation, such individuals are at increased risk of venous thromboembolism in the peri-operative period and require adequate anticoagulant prophylaxis until they are fully mobile.

Unfortunately, about one-quarter of cases of chronic thrombocytopenia fail to respond to these measures and must then be managed on the basis of their haemorrhagic risk. Other treatment strategies include alternative immunosuppressants, e.g. azathioprine, cyclosporin, vincristine and synthetic hormones, e.g. danazol.

Thrombocytopenia in pregnancy

Special consideration must be given to the management of thrombocytopenia in pregnancy.[32] Maternal thrombocytopenia is a frequent occurrence in pregnancy, the causes of which are set out in Table 6. The platelet count tends to fall in a normal pregnancy. Although mild thrombocytopenia (120–150 × 10^9 litre^{-1}) is not uncommon, it is important that more serious underlying disease is excluded.

Having eliminated the apparent thrombocytopenia associated with platelet clumping in the anticoagulant EDTA, the commonest cause is 'benign' gestational thrombocytopenia, which occurs in up to 7% of pregnancies. The platelet count rarely falls below 80 × 10^9 litre^{-1} and no intervention is, therefore, necessary as the condition is reversible after delivery.

When autoimmune thrombocytopenia is present in pregnancy, management is directed at maintaining a maternal platelet count above 50 × 10^9 litre^{-1} to minimize peripartum haemorrhage and prevent spontaneous fetal haemorrhage. Evidence of associated autoimmune disorders, such as the antiphospholipid syndrome, should be sought. In many cases, no intervention is necessary and vaginal delivery proceeds uneventfully, although epidural anaesthesia is contraindicated if the platelet count falls below 80 × 10^9 litre^{-1}. If the platelet count falls below 50 × 10^9 litre^{-1}, specific measures are required to prevent bleeding at delivery. Treatment options are corticosteroids and high-dose i.v. immunoglobulin (0.4 g kg^{-1} daily for 5 days) Where these modalities fail, consideration should be given to high-dose methylprednisolone and other immunosuppressants, such as azathioprine. Splenectomy should be a last resort in the presence of a gravid uterus, but is best performed before 28 weeks with the support of platelet transfusion.

The neonates of such severely affected mothers require careful surveillance for the first few days after delivery, as the nadir in the platelet count occurs from the second to the fifth day of postnatal life as the splenic circulation is established.

The thrombocytopenia and disseminated intravascular coagulation of obstetric complications such as pre-eclampsia will require specific transfusion support in line with the results of serial monitoring of the coagulation profile, with urgent delivery of the fetus to secure early resolution. More rarely, recovery may be delayed until a few days after the baby is delivered in the presence of maternal haemolysis with elevated liver enzymes and low platelets (HELLP) syndrome.

Thrombocytopenia as a feature of thrombotic thrombocytopenic purpura and the haemolytic uraemic syndrome is a rare event in pregnancy and the post-partum period. Additional features include microangiopathic haemolytic anaemia with fluctuating neurological signs and deteriorating renal function. Evidence of DIC is absent and prompt delivery does not expedite clinical resolution. Furthermore, platelet transfusion is contraindicated and urgent plasma exchange is required, replacing with fresh frozen plasma.

Massive transfusion

Massive transfusion involves the replacement of circulating blood volume within 24 h and often much more quickly. Stored red cells are deficient in functional platelets and plasma reduction effectively removes coagulation factors. Transfused red cells serve to dilute out the patient's native coagulation reserves.[7] These effects are exacerbated by the infusion of dextrans and/or starch. Specific transfusion of coagulation factors in the form of fresh frozen plasma[52] and platelet concentrate[35] should be guided by the results of the coagulation profile, which must be repeated until haemostasis is achieved.

Each unit of blood is collected from the donor in 63 ml of anticoagulant (citrate phosphate dextrose with adenine), and higher volumes transfused lead to citrate toxicity with associated hypocalcaemia. In emergency situations, when blood is transfused rapidly, cooled red cells may also contribute to the patient's falling pH. Care must be exercised in the use of blood-warmers and pumps to ensure their proper function, in order to avoid haemolysis of red cells for transfusion. Potassium toxicity rarely presents problems in this situation except in neonates.

Extracorporeal circuits

Widely used for many years in cardiopulmonary bypass procedures, other extracorporeal techniques, such as intraoperative cell salvage, may now contribute to the support of various operative procedures. When platelets are exposed to large areas of inert material, some are retained there, rendering the patient thrombocytopenic. Reduced temperatures inhibit the production of thromboxane A_2 in some platelets, while others aggregate spontaneously and prematurely. Those platelets which do return to the patient's circulation may thus have been injured on their journey, for early sequestration in the spleen. For these reasons, the bleeding patient may benefit from platelet transfusion, irrespective of the postoperative platelet count after bypass procedures.

Anticoagulation administered to facilitate cardiopulmonary bypass procedures may also be associated with postoperative bleeding. Heparin is reversed by protamine sulphate,[9] which, in excess, gives rise to a consumptive coagulopathy. If neutralization is incomplete, active heparin may reappear in the circulation 2–6 h after operation as it is released from heparin–protamine complexes in the extravascular compartment.

Acquired inhibitors of coagulant factors

Whilst inhibitors occur quite frequently as IgG antibodies directed against transfused factor VIII concentrate, the occurrence of antibodies to coagulation factors *de novo* is a much rarer event.[20] These are diagnosed in the presence of a prolonged time in a coagulation screen which fails to be corrected on addition of normal plasma. Commonly associated with autoimmune disorders, drug reactions or the post-partum period, patients with inhibitors usually present with severe mucosal bleeding, whereas spontaneous haemarthrosis is uncommon. In the postoperative period, this may lead to wound haematoma and/or secondary haemorrhage. The principles of management are threefold: to treat any underlying cause; to restore the deficient coagulation factor; and to block the formation of its inhibitor. In acquired haemophilia, agents prescribed to achieve haemostasis include large doses of factor VIII concentrate of human origin and porcine factor VIII. When the titre of factor VIII inhibitor exceeds 100 units per millilitre, specific factor VIII concentrate is no longer effective. Attempts may then be made to secure haemostasis by bypassing factor VIII, using partly activated mixtures of vitamin K-dependent clotting factors (II, VII, 1X and X), although there is an associated thrombotic risk.

Such products include intermediate purity factor IX (9A, BPL), FEIBA (factor eight bypassing activity) (Immuno) and Autoplex (Baxter). Recombinant activated factor VII (rVIIa) may be effective when these plasma-derived products fail. Immunosuppression should be prescribed simultaneously, as high-dose steroids, i.v. immunoglobulin or alkylating agents. Where inhibitors arise in response to transfusion of factor concentrate, the relative risks and benefits must be considered carefully before any operative procedure is planned. Every effort must be made to suppress inhibitor formation before elective surgery is contemplated.

More recently, factor V inhibitors have been described following the application of topical fibrin glue and thrombin.

Intermediate coagulation disorders

These disorders are characterized by an inappropriate predisposition to both bleeding and clotting. Their pathology is usually associated with failure of one or more major organs or a multisystem disease process with variable expression.

Renal disease

In renal failure, a decrease in erythropoietin production gives rise to anaemia with a falling haematocrit. Together with acquired disorders of platelet adhesion and a platelet storage pool defect,[30] this leads to an increased bleeding time, which may sometimes be corrected by DDAVP.[31] The anaemia may be improved preoperatively using erythropoietin, with iron supplements as appropriate.[50]

By contrast, secondary polycythaemia as a result of renal disease is associated with a raised haematocrit and increased risk of thrombosis.

Liver disease

The liver is the production site of the majority of coagulation factors, hence disturbance of liver function may lead to a tendency to bleeding. Where cirrhosis ensues, disturbance of liver architecture predisposes[5] to a chronic consumptive coagulopathy.[10] If this is then complicated by portal hypertension, splenic sequestration contributes to the thrombocytopenia as another source of bleeding. Ascitic fluid produced in cirrhosis has been shown to contain procoagulants, including tissue factor, factor X activator, collagen and endotoxin, which predispose to thrombosis after shunting.

Systemic lupus erythematosus

Two major coagulation problems occur within the clinical spectrum of systemic lupus erythematosus. A common association is immune thrombocytopenia; the bleeding diathesis associated with this problem is discussed above. Systemic lupus erythematosus in some individuals is also associated with the production of an antibody to glycoprotein Ib, found on the platelet membrane. This may give rise to an antiphospholipid syndrome (APS), an acquired procoagulant state characterized by recurrent venous and arterial thromboembolism.[18] Cerebral episodes present a particular problem in APS, and recurrent miscarriage is a common presentation in young women with this condition. The antibody, which is known as the lupus anticoagulant, is associated with a prolonged activated partial thromboplastin time which fails to correct with normal plasma, indicating the presence of an inhibitor.

Anticardiolipin antibodies are also increased. Long-term oral anticoagulant therapy is prescribed to control symptoms. Successful outcome of pregnancy has been achieved with the prescription of aspirin and low molecular weight heparin prophylaxis. Clearly, these patients present a very high risk of thrombosis in the peri-operative period and are best managed with therapeutic doses of i.v. unfractionated heparin.

Haematological malignancy

Disseminated intravascular coagulation in acute promyelocytic leukaemia has been discussed already. Far more common are the myeloproliferative disorders, which are caused by excessive activity of the pluripotential stem cell or lack of negative feedback in its production and differentiation. Diseases in this group include polycythaemia vera, chronic granulocytic leukaemia, essential thrombocytosis and myelofibrosis. Their course is chronic and often associated with a thrombocytosis. Although this creates an increased risk of thrombosis in the peri-operative period, necessitating anticoagulant prophylaxis, the abnormal platelets produced by the defective stem cells may not function normally in response to the blood loss of surgery. Every effort should be made to restore the blood count parameters to normal before elective procedures, but abnormal bleeding, even in the presence of a normal or raised platelet count, may be controlled by transfusion of platelet concentrate[35] in such patients.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (type 2) is a disorder in which a falling platelet count occurs in association with a progressive thrombotic tendency, which affects large vessels, both arterial and venous.[11 24] More than half of those affected sustain limb amputation and the mortality is high. The thrombocytopenia is caused by a specific antibody to platelet factor 4 which promotes platelet aggregation to initiate thrombosis. It usually occurs as an acquired primary immune state between 5 and 10 days after heparin therapy is initiated, more commonly after therapeutic doses of the unfractionated drug than low molecular weight heparin.[49] It may occur before 5 days as a secondary response on inadvertent re-exposure to heparin. Although a number of antibody detection tests have been set up, the diagnosis is essentially clinical and must be followed by immediate withdrawal of heparin and anticoagulation with a heparinoid such as danaparoid or lepirudin, as parenteral therapy, to cover the introduction of oral coumarins. Should the same patient require surgery in the future, heparin must be avoided in favour of the heparinoids described above.[17]

The hypercoagulable state: hereditary thrombophilia

Table 7 Genetic risk factors for venous thromboembolism

Anticoagulant deficiency or defect	Antithrombin (formerly antithrombin III) Protein C Protein S
Abnormal coagulant protein	Factor V Leiden Prothrombin gene mutation (20210) Dysfibrinogen
Increased procoagulant	ProthrombinFactor VIII
Abnormal metabolism	Hyperhomocysteinaemia

Over the last 20 yr, a large amount of information has accumulated about factors contributing to a hypercoagulable state.[27 37] Although many of these are associated with lifestyle risk factors such as obesity, immobility and smoking, or prothrombotic states such as malignancy, increased viscosity and pregnancy, there are a number of hereditary factors the presence of which places particular families at risk. Genetic risk factors recognized in the aetiology of venous thromboembolism are given in Table 7. The risks of venous thromboembolism in the peri-operative period are well recognized and those with heritable thrombophilia will benefit from enhanced anticoagulant prophylaxis. Antithrombin III, protein C and protein S deficiencies were first identified for their prothrombotic significance, since these proteins usually act as inhibitors of the formation of the 'tenase' complex in coagulation. Antithrombin III deficiency is the least common but the most serious. Specific concentrates of both antithrombin III and protein C are available for transfusion to cover elective surgical procedures.

More recently, it was recognized that some individuals with adequate amounts of protein C antigen appear to have an activated protein C resistance which prevents protein C from acting as an inhibitor of coagulation *in vitro*. In many cases, this is caused by the presence of a variant of one of the coagulant proteins, factor V, known as factor V Leiden, which is mutated at the site for protein C interaction.[4] This is present in 5% of the population but more frequently in those with venous thromboembolism. Similarly, a variant which impairs control of the 'prothrombinase' complex is programmed by the prothrombin gene mutation 20210.[36] This occurs in 2% of the population but more frequently in those with venous thromboembolism, and is, with the factor V Leiden gene mutation, an additive risk factor.

More recently, a clear relationship has been established between arterial thrombosis and hyperhomocysteinaemia,[43] the latter being common in individuals with a variant of the enzyme methylene tetrahydrofolate reductase, particularly in the homozygous state, the prevalence being approximately 12%.[14]

The discrepancy between recorded thrombosis and the prevalence of these genetic variants in the general population indicates that, in most cases, other factors play a part in their causation. In terms of management, therefore, treatment is directed at the history of clinical events rather than the identification of isolated risk factors. Although the

Table 8 Comparison of properties of unfractionated heparin and low molecular weight heparin

Property	Unfractionated heparin	Low molecular weight heparin
Mean molecular weight (Raye)	15 (4–30) kDa	4.5 (2–10) kDa
Saccharide units (mean)	40–50	13–22
Relative activity anti-X^a/anti II$_a$	1.1	3.1 (2.1–4.1)
Inhibits platelet function	Yes	No
Bioavailability at low dose	50%	100%
Elimination	Hepatic and renal	Renal
Half-life of anti X^a activity		
Intravenously	1 h	2 h
Subcutaneously	2 h	4 h
Monitoring	Yes	No (except in renal failure and pregnancy)
Frequency of heparin-induced thrombocytopenia	High	Low
Osteoporosis on prolonged therapy	Yes	Yes
Risk of haemorrhage	Present	Reduced

presence of additional prothrombotic markers may be considered in the risk assessment used to plan anticoagulant prophylaxis in the peri-operative period, this rarely influences decisions about the prescription of long-term oral anticoagulant therapy. A first episode of venous thromboembolism is treated with a discrete course of anticoagulant therapy followed by thrombophilia screening a few weeks after the end of treatment. Only after a second spontaneous event is it usual to recommend life-long therapy.[51]

Anticoagulant management in the peri-operative period

Increasing numbers of patients now receive oral anticoagulant therapy to reduce their risk of stroke from atrial fibrillation and other cardiac disorders.[51] Minor surgery, including dental extraction and endoscopy with biopsy, may be undertaken safely with an international normalised ratio of 2.5 or less. Many anticoagulant patients may have coumarin stopped for a few days without harm.

There remain two major risk groups who will require conversion to i.v. unfractionated heparin in the peri-operative period to maintain therapeutic anticoagulation in the absence of postoperative bleeding.[21 26] These are patients with mechanical cardiac valve prostheses[45] and those with a history of acute venous thromboembolism within the previous 4 weeks or during a current pregnancy. The heparin must be stopped 6 h before the operation and restart 12 h after operation, and oral coumarin should be reintroduced as soon as possible thereafter.[26] Epidural anaesthesia is best avoided for those on therapeutic heparin.[6]

Even in the absence of any known thrombophilia markers, surgical patients are at increased risk of venous thromboembolism as a result of their immobility and the postoperative inflammatory response.[40 44] All should be assessed for their individual risk in relation to the procedure planned, and advised about the importance of leg exercise and early mobilization. Appropriate antiembolism hosiery should be fitted. Anticoagulant prophylaxis with subcutaneous unfractionated heparin will cover moderate- and high-risk surgery, including operations on pelvic sites and arthroplasty, but very high-risk patients may benefit from a prophylactic dose of a low molecular weight heparin Such prophylaxis is not usually associated with increased bleeding in the peri-operative period, but should not be prescribed for neurosurgical procedures.

In recent years, a number of low molecular weight heparins (LMWH) have been produced with specific anti-Xa activity.[19] Administered by the subcutaneous route, they are as effective as i.v. unfractionated heparin (UFH) in treating acute venous thromboembolism.[28] The comparative properties of LMWH and UFH are described in Table 8. Although all are licensed in the UK for deep venous thrombosis, only one LMWH (tinzaparin) has a licence recommendation for the treatment of pulmonary embolism.[41] In most cases, their use requires only monitoring of the platelet count to exclude heparin-induced thrombocytopenia, although anti-Xa concentrations require checking in patients with renal failure and in the critically ill. It has been suggested that haemorrhagic complications are less frequent with LMWH than UFH because of their specificity of action.[23]

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SHORT COMMUNICATIONS

Within-breath arterial Po_2 oscillations in an experimental model of acute respiratory distress syndrome

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Tidal ventilation causes within-breath oscillations in alveolar oxygen concentration, with an amplitude which depends on the prevailing ventilator settings. These alveolar oxygen oscillations are transmitted to arterial oxygen tension, Pa_{O_2}, but with an amplitude which now depends upon the magnitude of venous admixture or true shunt, $\dot{Q}s/\dot{Q}T$. We investigated the effect of positive end-expiratory pressure (PEEP) on the amplitude of the Pa_{O_2} oscillations, using an atelectasis model of shunt. Blood Pa_{O_2} was measured on-line with an intravascular Pa_{O_2} sensor, which had a 2–4 s response time (10–90%). The magnitude of the time-varying Pa_{O_2} oscillation was titrated against applied PEEP while tidal volume, respiratory rate and inspired oxygen concentration were kept constant. The amplitude of the Pa_{O_2} oscillation, ΔPa_{O_2}, and the mean Pa_{O_2} value varied with the level of PEEP applied. At zero PEEP, both the amplitude and the mean were at their lowest values. As PEEP was increased to 1.5 kPa, both ΔPa_{O_2} and the mean Pa_{O_2} increased to a maximum. Thereafter, the mean Pa_{O_2} increased but ΔPa_{O_2} decreased. Clear oscillations of Pa_{O_2} were seen even at the lowest mean Pa_{O_2}, 9.5 kPa. Conventional respiratory models of venous admixture predict that these Pa_{O_2} oscillations will be reduced by the steep part of the oxyhaemoglobin dissociation curve if a constant pulmonary shunt exists throughout the whole respiratory cycle. The facts that the Pa_{O_2} oscillations occurred at all mean Pa_{O_2} values and that their amplitude increased with increasing PEEP suggest that Qs/QT, in the atelectasis model, varies between end-expiration and end-inspiration, having a much lower value during inspiration than during expiration.

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Krogh and Lindhard, in 1914,[1] hinted that alveolar and arterial oxygen tensions, PA_{O_2} and Pa_{O_2} respectively, could fluctuate during the respiratory cycle. Bergman, in 1961,[2] confirmed this hypothesis with an animal model using arterial saturation, Sa_{O_2}, as a proxy for Pa_{O_2}. Although Bergman was not able to measure Pa_{O_2} continuously, he hypothesized that fluctuations in Sa_{O_2} during the respiratory cycle might be due to the pulmonary shunt fraction ($\dot{Q}s/\dot{Q}T$) changing between the inspiratory and expiratory phases of the respiratory cycle. Further isolated studies over the past 30 yr have shown that oscillations in arterial oxygen tension, cotemporaneous with the respiratory cycle, do occur and that they are most apparent in the presence of hypoxaemia or significant venous admixture.[3] [4] The origin of these oscillations, with peak-to-peak amplitude denoted by ΔPa_{O_2}, are thought to be in the complex interaction between the continuous process of gas exchange and the tidal process of the ventilation respiratory cycle.[5–7] We considered that if variations in $\dot{Q}s/\dot{Q}T$ caused by atelectasis occurring during expiration and alveolar reopening during inspiration, did occur in the lung, then the amplitude of the oscillations would be sensitive to the application of PEEP when both the inspired oxygen fraction (FI_{O_2}) and the ventilator settings were kept constant. We assessed the effect of PEEP on

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Table 1 The effect of increasing (upper of each pair of rows) and decreasing (lower row) PEEP on blood gases, oxygen saturation, peak airway pressure, shunt fraction, cardiac output and arterial blood pressure. The mean (SD) is shown for seven animals unless indicated by a superscript number. Blood-gas values were corrected to 38°C. Statistical significance was assessed using the paired Student's *t*-test (unpaired when *n* not equal) *Prelavage value different ($P<0.05$) from the postlavage value, **value of the variable at 0 PEEP significantly ($P<0.05$) altered by 2 kPa PEEP, ***Value of the variable during lung inflation at a given PEEP level significantly different ($P<0\ 05$) from the value during deflation. Otherwise no statistical differences were found

	Before lavage	**After lavage PEEP (kPa)**				
		0	**0.5**	**1**	**1.5**	**2**
Pa_{O_2} (kPa)	56.6 2.5	9.5 (0 7)*	11 8 (1 6)	24 5 (12.7)	41.9 (9.1)	49 6 (7 1)**
		8 3 (1.1)^6 ***	10 1 (1 0)***	16.5 (3.9)^6	35.9 (8.8)	
Pv_{O_2} (kPa)	8.8 (1.3)	6.5 (1.1)*	7.0 (1.1)	8 0 (1.1)	8.8 (2 5)	7 9 (1 4)**
		5 8 (0.9)***	6.4 (0.6)	7 6 (0.8)	7 9 (1 3)	
Pa_{CO_2} (kPa)	4.2 (0.5)	5 4 (1.1*	5.5 (1.2)	5 0 (1.1)	4.9 (1 1)	5.2 (1.3)
		5 7 (1.7)	5.5 (1.4)	5 2 (1.3)	4.9 (1.3)	
Pv_{CO_2} (kPa)	4.8 (0.3)	6 1 (0.8)*	5.8 (1.0)	5 5 (1.5)	6.1 (1 1)	6.6 (1 5)
		7 1 (1 5)	6.7 (1.7)	6 8 (1.6)	6.1 (1 5)	
Sa_{O_2} (%)	100 (0)	82 (5)*	89 (6)	97 (3)	99 (1)	100 (0)**
		72 (6)***	81 (6)	92 (5)	98 (2)	
Sv_{O_2}(%)	85 (5)	58 (13)*	62 (13)	70 (10)	70 (9)	66 (11)**
		47 (8)	55 (4)	65 (6)	66 (9)	
Peak airway pressure (kPa)	1 7 (0.4)	2.8 (0 3)*	3.0 (0 3)	3.4 (0 2)	4.7 (0.4)	5 8 (0.7)**
		2 7 (0 1)	2.9 (0.1)	3.2 (0.1)	4 3 (0 5)^6	
Shunt fraction (%)	6 (1)^6	53 (16)*	38 (11)^6	22 (11)	15 (16)	6 (4)**
		61 (11)	46 (9)	25 (9)^6	12 (5)	
Cardiac output (litre min^{-1})^6	2.4 (0.7)	2.1 (0.7)	2.0 (0.4)	1 7 (0 4)^5	1.4 (0.3)	1.1 (0 2)**
		1.7 (0.4)	1.7 (0.5)	1.4 (0.2)	1 3 (0 3)	
Systolic pressure (kPa)^6	20 6 (1 5)	13.4 (2 8)*	13.2 (2.3)	12.6 (2.8)	12 0 (2 4)	11.0 (0 2)**
		12 6 (2 8)	12.2 (2.4)	12.4 (2 8)	11.4 (2.9)	
Diastolic pressure (kPa)^6	15.8 (2.0)	8.5 (3.5)*	8.1 (2 5)	8.0 (2 5)	7.6 (2 5)	6 4 (2.7)
		7 3 (2 5)	7.6 (3 3)	7.2 (2 9)	6.4 (2.9)	

ΔPa_{O_2} in an experimental model of atelectasis [simulating acute respiratory distress syndrome (ARDS)] which developed moderate to severe levels of pulmonary shunt.

Methods and results

In seven adult female dogs (weight range 10.4–13.3 kg), anaesthesia was induced by i.v. pentobarbitone sodium (60 mg ml^{-1}) and maintained by infusion (60–180 mg h^{-1}). The surgical preparation was performed as described elsewhere.[8]

A prototype intravascular Po_2 sensor (IE Sensors, Salt Lake City, Utah, USA) was inserted into the aorta and left to stabilize. This Clark-type amperometric sensor had a 10–90% response time of 2–4 s. Fibre optic pulmonary artery catheters (Opticath Catheter; Abbott Critical Care Systems, Chicago, Illinois, USA) were used to measure mixed venous blood oxygen saturation continuously using the principle of reflectance spectroscopy (Oximetric 3; Abbott Critical Care Systems). Intermittent measurement of blood gases and pH were made using a blood-gas analyser (ABL 330; Radiometer, Copenhagen, Denmark), and the same blood sample was used to measure other blood variables by co-oximetry (OSM 3, Radiometer). Cardiac output, $\dot{Q}T$, was measured by thermodilution (Oximetric 3, Abbott Critical Care Systems). The value of $\dot{Q}S/\dot{Q}T$ was calculated conventionally using the FI_{O_2}, blood gas and saturation data, assuming a respiratory quotient of 0.8.

Correct positioning of the Po_2 sensor in the aorta was assessed by observing the blood pressure tracing from the sensor's blood sampling port and by a stable mean Pa_{O_2}. The Po_2 sensor was calibrated against drawn heparinized arterial blood using the blood-gas analyser. Inspired and expired oxygen concentrations were measured, at the end of the tracheal tube, using a respiratory Quadrupole mass spectrometer (VG Quadrupoles, Middlewich, UK).

Throughout the study, the mechanically ventilated animals received a constant mean (SD) inspired FI_{O_2} of 0.72 (0.01). Tidal volume and respiratory rate were kept constant during each individual study, but ranged from 0.25 to 0.30 litres and 11 to 13 breaths min^{-1}, respectively, between animals to maintain an end-expired carbon dioxide concentration of 4.7 (0.6)% v/v. After surgery, a stabilization period of 1–2 h was allowed and baseline (prelavage) values were recorded (Table 1). Bronchopulmonary lavage was performed to deplete the lung surfactant, inducing a large pulmonary shunt. The lavage procedure was repeated, typically 10–20 times, until Pa_{O_2} had decreased from 57 to 10 kPa (Table 1). This procedure produced a typical initial shunt fraction, $\dot{Q}S/\dot{Q}T$, of 53% (SD 16%).

When the mean Pa_{O_2} was stable, a set of observations was taken, followed by simultaneous venous and arterial blood samples. The time-varying Pa_{O_2} signal was recorded over 30

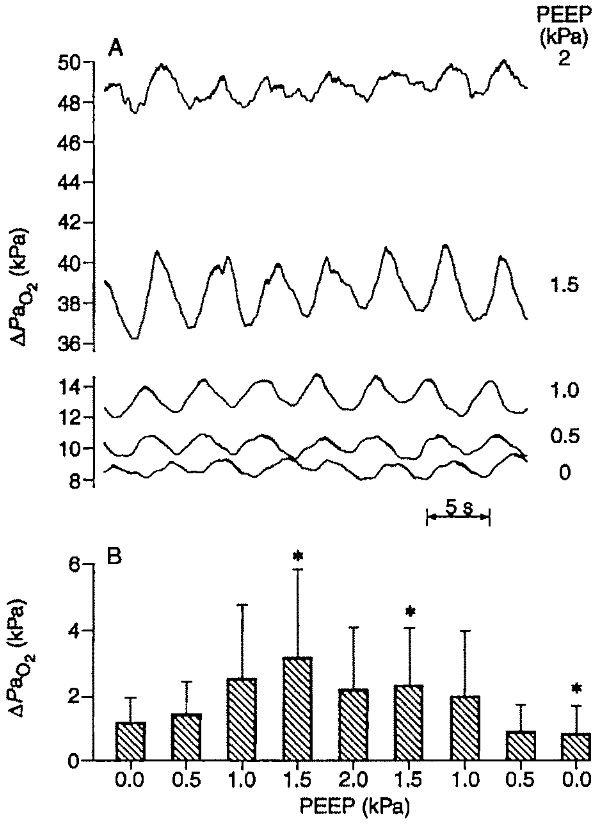

Fig 1 (A) Breath-by-breath oscillations in Pa_{O_2} (with peak-to-trough amplitude ΔPa_{O_2}) at different levels of PEEP, and at a constant F_{IO_2} of 0.72, recorded by an intravascular Pa_{O_2} sensor with a 10–90% response time of 2–4 s The Pa_{O_2} is at its peak at the end of inspiration and at its lowest at the end of expiration. Data from a single animal are shown. The respiratory rate was 11 breaths min^{-1}, and the tidal volume was kept constant at 310 ml There is no phase (time) relationship between any of the above time-varying Pa_{O_2} traces shown at the various PEEP levels (B) The effects of incremental changes in PEEP on ΔPa_{O_2} from 0 to 2 kPa and decremental PEEP from 2 to 0 kPa. The mean (SD) for seven animals is shown

breaths by computer. This procedure was repeated every 20 min with 0.5 kPa increments of PEEP from 0 to 2 kPa, followed by a return to zero PEEP (ZEEP) in decrements of 0.5 kPa.

Results (Table 1 and Fig. 1) are expressed as mean (SD), and the statistical analysis was by one-way analysis of variance with repeated measurements. When this analysis showed significance, *post hoc* comparisons of the means were made by Scheffé's test. A P value less than 0.05 was considered as significant. Table 1 shows the overall effect of increasing and decreasing PEEP on blood gases, oxygen saturation, cardiac output, shunt fraction and arterial blood pressure. The table also shows the conventional pulmonary blood-flow shunt fraction calculated at each PEEP level. Bronchopulmonary lavage reduced the mean (prelavage) Pa_{O_2} by 47 kPa and the mean $P\bar{v}_{O_2}$ by 2.3 kPa. At the initial low mean Pa_{O_2}, 9.5 (0.7) kPa, the Pa_{O_2} signal began to oscillate about its mean value with an amplitude of 1.2 (0.8) kPa, and both the mean Pa_{O_2} and its oscillation amplitude began to increase as PEEP was imposed. Figure 1A shows typical results taken from a single animal study. It must be noted that the $Pa_{O_2}(t)$ time-varying tracings presented in this figure are not related to each other on the time axis, and no physiological inference can be made from the time-phase differences of these traces. Figure 1B shows the effect of incremental changes on ΔPa_{O_2} (mean (SD)) for all the studies, as PEEP was firstly increased from 0 to 2 kPa and then decreased from 2 to 0 kPa. Each individual study showed the same effects of PEEP on ΔPa_{O_2} as those illustrated in Fig. 1, namely that (i) as PEEP was initially increased, both the mean Pa_{O_2} and ΔPa_{O_2} increased; but that (ii) ΔPa_{O_2} began to decrease after a certain PEEP value was reached, although the mean Pa_{O_2} continued to rise. This pattern was reversed as PEEP was reduced back to its baseline (ZEEP) level. In all instances, the Pa_{O_2} oscillations followed the ventilator frequency, and appeared to become maximal at the end of inspiration and minimal at the end of expiration. There was also a transport lag between the ventilator inspiratory–expiratory phases and the Pa_{O_2} oscillations.

Comments

There were two main findings of this study. First, an experimental animal model of ARDS was associated with significant oscillations in Pa_{O_2} linked with the respiratory cycle. Secondly, the peak-to-peak amplitude of these fluctuations, ΔPa_{O_2}, was dependent upon the level of PEEP applied to the damaged lungs, the magnitude of the amplitude increasing up to 3 kPa with increasing PEEP. The true *in vivo* Pa_{O_2} oscillations were probably considerably greater than this because the intravascular Pa_{O_2} sensors had a 10–90% response time of only 2–4 s. This would have attenuated the rapidly changing true *in vivo* arterial P_{O_2} signals. A rough calculation of the true magnitude of the Pa_{O_2} oscillations can be derived from the knowledge of the P_{O_2} sensor response time, the respiratory rate, by approximating the inspiration:expiration ratio to 1:1 and then using the formula of Arieli and Van Liew[9] to calculate the attenuation of the physiological Pa_{O_2} signal due to the sensor membrane. This rough calculation suggests that the *in vivo* Pa_{O_2} peak-to-trough oscillations are up to three times greater than those recorded by the IE Sensors Inc. intravascular P_{O_2} sensors, shown in Fig. 1A.

Both Purves and the Kreuzer group, in the 1960s and 1970s, reported respiratory-induced oscillations in arterial P_{O_2} in animal models.[3 4] These were a direct consequence of tidal ventilation fluctuations in alveolar gas oxygen tension, and had the same period as the ventilator setting. An increase in tidal volume or a decrease in ventilation frequency led to an increase in the amplitude of the Pa_{O_2} oscillations. These early studies ruled out the possibility that the effects of cyclical variations in arterial pressure, or blood flow, could produce the measured Pa_{O_2} fluctuations. In contrast to our own animal ARDS model, these earlier studies investigated these Pa_{O_2} oscillations only in the healthy lung.

Our own findings confirm those of previous authors, such as Bergman's report in 1961[2] of oscillations in arterial oxyhaemoglobin saturation, Sa_{O_2}, (when haemoglobin was not fully saturated) and, more recently, those of Elwell *et al.* in 1996,[11] which demonstrated that oscillations in arterial saturation occur with the induction of mild hypoxia. The results of Elwell *et al.* were explained by Lovell *et al.* in 1997,[11] who showed that changes in ventilator settings could alter the Sa_{O_2} oscillations. Bergman showed that the amplitude of the Sa_{O_2} oscillations diminished as haemoglobin became saturated, but he was not able to measure Pa_{O_2} on-line.[2] However, on the basis of his Sa_{O_2} studies, he hypothesized that the most likely explanation of his results was that pulmonary shunt varied during the respiratory cycle as a result of the lung collapsing during expiration and then reopening during positive-pressure inspiration.

Two problems need to be faced. These are that (i) the ΔPa_{O_2} amplitudes observed in our study were larger than would be expected in healthy lungs; and (ii) current knowledge suggests that Pa_{O_2} oscillations on the steep part of the oxyhaemoglobin association/dissociation curve are buffered by the shape of the curve describing the relationship of oxygen content with $P\mathrm{O}_2$. Significant Pa_{O_2} oscillations in this steep part of the curve could be caused by. (i) the presence of inhomogeneity in the lung ventilation–perfusion ratio induced by the pulmonary lavage; (ii) different degrees of atelectasis occurring in the lung during the inspiratory and expiratory phases of the respiratory cycle (the Bergman hypothesis); or (iii) a combination of both mechanisms, as they do not exclude one another.

We consider that, during inspiration, more alveoli are recruited, with a decrease in venous admixture (during inspiration) and consequently an increase in both the mean Pa_{O_2} and the $Pa_{\mathrm{O}_2}(t)$ time-varying oscillatory signal. During expiration, these recruited alveoli could collapse and contribute to an increased shunt fraction and, thus, a decrease in mean Pa_{O_2}. When PEEP was increased sufficiently to induce permanent recruitment during the expiratory phase, the overall Pa_{O_2} amplitude would decrease and the mean Pa_{O_2} rise. On the other hand, if shunt fraction was constant during both the inspiratory and expiratory phases of respiration (the conventional view of $\dot{Q}\mathrm{S}/\dot{Q}\mathrm{T}$) then the ΔPa_{O_2} oscillations would not appear at all at low mean Pa_{O_2} values because of the buffering capacity of oxyhaemoglobin in this region of the dissociation curve.

It now seems clear that Pa_{O_2} oscillations occur in the atelectatic lung, and that the application of PEEP not only elevates the mean arterial Pa_{O_2} but also affects the magnitude of the Pa_{O_2} oscillations superimposed on this mean. The effect of these oscillations in the clinical care setting is not clear.

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Spasmolytic effects of prostaglandin E_1 on serotonin-induced bronchoconstriction and pulmonary hypertension in dogs

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In this study, we simultaneously evaluated the spasmolytic effects of prostaglandin E_1 (PGE_1) on serotonin-induced bronchoconstriction and pulmonary hypertension. Eleven mongrel dogs (8–12 kg) anaesthetized with pentobarbital were assigned to two groups: saline (n=4) and PGE_1 (n=7). Bronchoconstriction and pulmonary hypertension were elicited with serotonin 10 μg kg^{-1} + 1 mg kg^{-1} h^{-1} and assessed as the percentage change in bronchial cross-sectional area (BCA) measured by bronchoscopy and pulmonary vascular resistance (PVR), respectively. Thirty minutes after starting the serotonin infusion, saline or PGE_1 0 (saline), 0.01, 0.1, 1.0 or 10 μg kg^{-1} i.v. was given. %BCA and %PVR (basal=100%) were assessed before and 30 min after serotonin, and 30 and 60 min after saline (saline group) or 5 min after each dose of PGE_1 (PGE_1 group). In the saline group, pulmonary hypertension and bronchoconstriction were stable. In the PGE_1 group, PGE_1 at ≥0.1 μg kg^{-1} significantly decreased %BCA and 10 μg kg^{-1} almost fully reversed the constriction (from mean (SEM) 56.2% (4.9%) to 94.4% (3.7%)). %PVR was significantly decreased at 10 μg kg^{-1} (from 230% (24%) to 176% (11%)) only. We suggest that PGE_1 may produce bronchodilation rather than pulmonary vasodilation.

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Prostaglandin E_1 (PGE_1) relaxes not only vascular smooth muscle but also airway smooth muscles.[1] It has been reported that 60–90% of PGE_1 is inactivated after one passage through the pulmonary circulation in dogs, cats, rabbits and humans.[2] Its rapid metabolism in the lung may limit its clinical use, so previous investigators have examined inhalational administration of PGE_1 (see reference [2] for details): it has been found that (i) this may be more effective than i.v. administration for antagonizing airway constriction; (ii) PGE_1 has bronchodilating effects in asthmatic patients but not in healthy volunteers, but it was concluded that inhalation of PGE_1 is unsuitable for therapeutic use in asthmatic patients as airway irritation occasionally induced bronchoconstriction; (iii) inhalation of PGE_1 *per se* sometimes produces bronchial constriction, as coughing and bronchospasm were observed in one of six asthmatic volunteers, but bronchodilation was observed in the remaining volunteers.

We have previously demonstrated that PGE_1 reverses histamine-induced bronchoconstriction dose-dependently.[2] A multicentre clinical trial has shown that liposomal PGE_1 improved oxygenation, increased lung compliance and decreased ventilator dependency in patients with acute respiratory distress syndrome (see reference 2). These findings suggest that i.v. PGE_1 may be effective in airway constriction.

PGE_1 has been reported to be useful for treating pulmonary hypertension.[3] In addition, several reports suggest that it may reduce experimental pulmonary hypertension[4]. However, Priebe reported that PGE_1 had no beneficial cardiopulmonary effects in a canine model of acute pulmonary hypertension.[5] The spasmolytic effects of PGE_1 in pulmonary hypertension thus remain controversial.

Serotonin (5-hydroxytryptamine, or 5HT) increases smooth muscle tone via 5HT receptors at low concentrations and via α-adrenoceptors at high concentrations.[6] Hence it simultaneously produces bronchoconstriction and pulmonary hypertension.

In this study, we examined whether PGE_1 reversed 5HT-induced bronchoconstriction and pulmonary hypertension.

Methods and Results

Following approval of our study protocol by the Animal Experiment Committee of the University of Hirosaki, 11

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mongrel dogs (8–12 kg) were anaesthetized with i.v. pentobarbital 30 mg kg^{-1} + 10 mg kg^{-1} h^{-1} and paralysed with pancuronium 0.2 mg kg^{-1} h^{-1}. The trachea was intubated using a special tracheal tube (Univent tube; Fuji System, Tokyo, Japan) with an additional small lumen for insertion of a superfine fibreoptic bronchoscope (outer diameter 2.2 mm; OES Angiofibrescope AF type 22A; Olympus, Tokyo, Japan). The lungs were mechanically ventilated with oxygen using a respirator (Servoventilator 900C; Siemens AB, Elema, Sweden) and the end-tidal carbon dioxide concentration maintained at 4.0–4.5%. A pulmonary artery catheter (CCO thermodilution catheter Model 139H 7.5F; Baxter Healthcare Corporation, CA, USA) was inserted through a sheath into the femoral vein to monitor pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) and cardiac output and to administer drugs and fluid (lactate Ringer's solution at 4 ml kg^{-1} h^{-1}). Cardiac output was measured continuously using a Vigilance monitor (Model VGSSYS; Baxter Healthcare, Corporation, Irvine, CA, USA). The femoral artery was cannulated to monitor systemic arterial pressure.

Airway tone was evaluated as bronchial cross-sectional area (BCA) determined by our bronchoscopic method as previously reported.[27] Briefly, the BCA at the third bifurcation of the right lung was continuously monitored through the bronchoscope, and the area during the end-expiratory pause was measured using image analysis software (NIH Image program written by Wayne Rasband at the US National Institutes of Health). Pulmonary vascular tone was assessed as pulmonary vascular resistance (PVR). Changes in BCA and PVR were expressed as a percentage of the basal value before 5HT infusion.

Bronchoconstriction and pulmonary hypertension were elicited with 5HT infusion (10 µg kg^{-1} +1 mg kg^{-1} h^{-1}) via the pulmonary artery catheter. Thirty minutes later, when stable pulmonary hypertension and bronchoconstriction was achieved, seven dogs were subsequently given each dose of PGE$_1$ in the following order: 0 (saline), 0.01, 0.1, 1.0 and 10 µg kg^{-1} (PGE$_1$ group) and four dogs were given saline only (saline group). BCA and PVR were assessed before and 30 min after the 5HT infusion started and 5 min after administration of each dose of PGE$_1$ in the PGE$_1$ group. At least 15 min elapsed between each administration. In the saline group, these variables were assessed before and 30 min after the 5HT infusion started, and 30 and 60 min after saline i.v.

Arterial blood (6 ml) was collected through the femoral artery catheter into syringes containing EDTA simultaneously with BCA and PVR assessment, immediately centrifuged at 3000 r.p.m. (1700 *g*) for 10 min at –10°C and then the plasma was separated and kept frozen at –70°C until catecholamine assay. Plasma catecholamine concentrations were determined by high performance liquid chromatography with electrochemical detection. The assay coefficients of variation for epinephrine and norepinephrine were 3.31% and 2.93%, respectively.

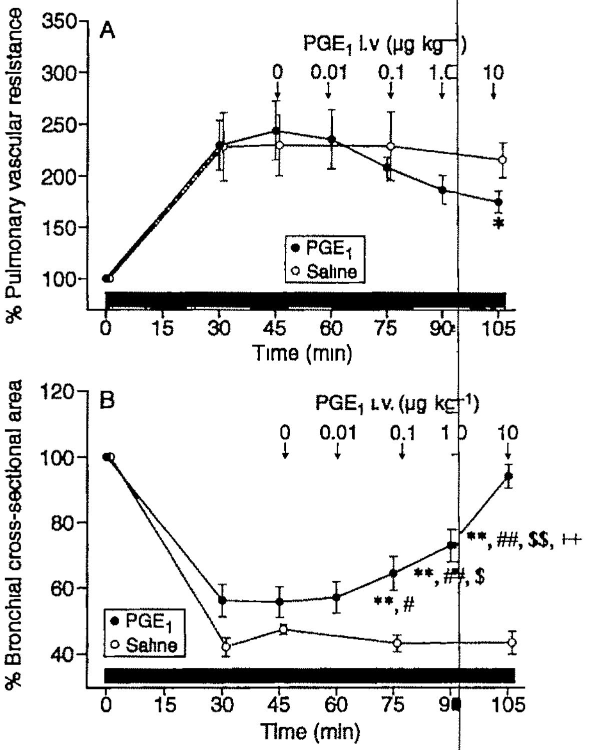

Fig 1 Effects of prostaglandin E$_1$ on 5HT-induced pulmonary hypertension (A) and bronchoconstriction (B) Application of 5HT (10 µg kg^{-1} + 1.0 mg kg^{-1} h^{-1}) is indicated by the solid bar *, # $ and + indicate $P<0.05$ and **, ##, $$ and ++ indicate $P<0.01$ compared with 0 (saline) and PGE$_1$ 0.01, 0.1 and 1.0 µg kg^{-1}, respectively All values are expressed as mean±SEM

Data are shown as mean (95% confidence interval) except in Figure 1. Statistical analyses were performed by repeated measure ANOVA followed by Fisher's protected least significant difference test. $P<0.05$ was considered significant.

5HT decreased %BCA by 40–60% and increased %PVR to about 230% (Figure 1). In the saline group, these values persisted until the end of the experiment. In the PGE$_1$ group, PGE$_1$ 10 µg kg^{-1} produced a significant reduction in %PVR (Figure 1A). In contrast, %BCA increased dose-dependently, such that PGE$_1$ 10 µg kg^{-1} almost fully reversed the constriction produced by 5HT (Figure 1B). Plasma epinephrine increased significantly from 165 (104–227) to 277 (50–503) pg ml^{-1} after PGE$_1$ 10 µg kg^{-1} i.v.

5HT did not significantly change systemic haemodynamic variables, while PAP was significantly increased. PGE$_1$ 10 µg kg^{-1} significantly decreased the following haemodynamic variables during 5HT infusion: systematic vascular resistance from 4274 (3345–5202) to 3338 (2608–4067, $P<0.01$) dynes·s cm^{-5} and mean arterial pressure from 127 (90–164) to 110 (78–143, $P<0.01$) mm Hg, whereas mean PAP did not change significantly (decreasing from 34 (28–39) to 31 (24–37) mm Hg).

Comments

Our results data show that PGE_1 attenuated 5HT-induced bronchoconstriction. Similarly, we have previously observed that PGE_1 also antagonized histamine-induced bronchoconstriction.[2] As PGE_1 is a an EP_2 receptor agonist, adenylate cyclase is activated to increase intracellular cAMP concentrations which produces airway smooth muscle relaxation.[1] Therefore, increased intracellular cAMP may contribute to the observed spasmolytic effects.

In the present study, plasma epinephrine slightly but significantly increased after administration of PGE_1 10 μg kg^{-1}. This suggests that PGE_1-induced systemic vasodilation increases sympathetic activity although PGE_1 attenuates arterial baroreceptor reflexes.[8] As circulating catecholamine concentration is one of the most important factors controlling airway tone,[9] catecholamine release may also be involved in the observed bronchodilation. However, as PGE_1 0.1 and 1.0 μg kg^{-1} produced significant bronchodilation without increases in plasma catecholamines, PGE_1 may have direct bronchodilatory effects.

PGE_1 has been used clinically for the treatment of pulmonary hypertension.[3] Fullerton and colleagues[10] have also shown a direct relaxant effect of PGE_1 on isolated rat pulmonary artery rings. In the present study, PGE_1 10 μg kg^{-1} significantly attenuated pulmonary hypertension although at $\leq$1.0 μg kg^{-1} PGE_1 was ineffective. However, as the catabolism of PGE_1 in the lungs of dogs is about six times that in humans,[2] clinically relevant doses may not attenuate pulmonary hypertension. Consistent with this, several reports[5] suggest that PGE_1 does not attenuate pulmonary hypertension by pulmonary vasodilation.

In conclusion, the present study indicates that clinically relevant doses of PGE_1 may produce direct bronchodilation, but not pulmonary vasodilation.

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Influence of airway-occluding instruments on airway pressure during jet ventilation for rigid bronchoscopy

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We measured changes in airway pressure (P_{aw}) caused by microsurgical instruments introduced into a rigid bronchoscope during high frequency jet ventilation (HFJV). With approval of the

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institutional Ethics Committee, 10 adults undergoing elective tracheobronchial endoscopy and endosonography during general anaesthesia were investigated. Inflation of an endosonography probe balloon in the left main stem bronchus caused airway obstruction. Pressure measurements proximal and distal to the obstruction were compared after three degrees of obstruction (0%, 50% and 90%) and with two different driving pressure settings. Airway obstruction increased the mean (SD) peak inspiratory pressure (PIP) from 7.5 (2.6) to 9.5 (3.5) mm Hg for 2 atm (P=0.0008) and from 9.7 (3.7) to 13.0 (5.1) mm Hg for 3 atm (P=0.0001). Airway obstruction did not alter peripheral PIP (7.2 (4.1) to 7.1 (3.7) mm Hg for 2 atm and 8.8 (4.3) to 9.4 (5.2) mm for 3 atm), but resulted in an end-expiratory pressure (EEP) beyond the narrowing being significantly greater than in the unobstructed airway (2.5 (3.4) to 5.5 (3.7) mm Hg for 2 atm; P=0.0005) and 3.2 (3.6) to 8.0 (4.3) mm for 3 atm; P<0.0001). Severe airway narrowing increases inspiratory pressure proximal and expiratory pressure distal to the obstruction in relation to the applied driving pressure. Since the distal EEP never exceeded PIP, even near-total airway obstruction should not cause severe lung distension or barotrauma in subjects with normal lungs.

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High frequency jet ventilation (HFJV) for rigid bronchoscopy is a convenient method that gives optimal visibility and easy access of diagnostic and surgical instruments to the airway, mainly because HFJV does not require a sealed airway. In constrast, the rigid bronchoscope must be kept open to the surrounding atmosphere to allow passive exhalation of the insufflated gas. Unless the egress of gas is impaired, inadvertent airway pressure (P_{aw}) elevation and lung distension are unlikely. However, there is a risk of airway obstruction when instruments are introduced into the bronchoscope. A newly developed probe for tracheobronchial endosonography, recently introduced for scanning of mediastinal structures, to assess lung tumours and affected lymph nodes, is such an instrument.[1 2] The tip of this probe has an expandable balloon which is filled with water as a transmission medium. To obtain the image, the balloon is expanded until sufficient contact is achieved between probe and airway wall. During inflation of the balloon, the airway is progressively obstructed; there is a risk that air will be trapped in the lung supplied by the obstructed airway.[3 4] The purpose of this study was to assess proximal and distal P_{aw} during progressive airway occlusion caused by intermittent inflation of the endosonography probe.

Methods and Results

Following approval by the institutional ethical committee and informed consent, 10 adults undergoing elective diagnostic or interventional tracheobronchial endoscopy and endosonography under general anaesthesia were enrolled. All patients received total intravenous anaesthesia with propofol, remifentanil and succinylcholine. HFJV was applied with an AMS 1000 jet ventilator (Acutronic Medical Instruments, Hirzel, Switzerland) via the jet port at the proximal end of a rigid bronchoscope (Karl Storz, Tuttlingen, Germany). Monitoring consisted of electrocardiography, non-invasive measurement of arterial pressure and pulse oximetry.

After insertion of the rigid bronchoscope, the endosonography probe was placed in the main left bronchus, where the artificial airway obstruction was to be created. Proximal and distal P_{aw} were measured with sensors derived from standard intravascular pressure measurement equipment, consisting of transducers and water-filled tubing. The proximal P_{aw} sensor was located in the tip of a steel tube with an internal diameter of 1.0 mm, which was introduced into the light guide channel of the bronchoscope. The distal P_{aw} was measured through a Cavafix Certo 358 catheter (B. Braun, Melsungen, Germany), internal diameter of 1.1 mm, which was placed with its tip into the left mainstem bronchus 10 cm distal to the tip of the bronchoscope. The validity of intratracheal P_{aw} measurement as an approximation for alveolar pressure was shown in previous investigations.[5] Both transducers were placed at the xiphoid level.

Airway obstruction was created by gradually filling the balloon of the endosonography probe, so that obstruction increased steadily from 0% to 100% over an 8 s period (Figure 1). P_{aw} was recorded throughout the balloon expansion. Three specific levels of obstruction, 0%, 50%

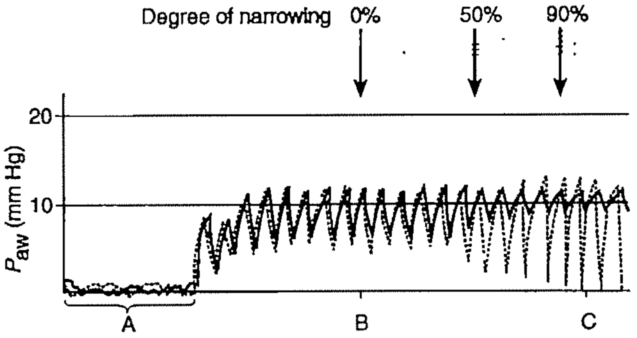

Fig 1 Proximal (dotted line) and distal (solid line) airway pressure (P_{aw}) in patient no 6 during increasing obstruction of the airway: Period A: apnoea during zeroing of both pressure sensors, period B: beginning of expansion of endosonography probe balloon; period C: complete occlusion of the airway.

Table 1 Biometrical and clinical data (mean (SD)) VC=vital capacity; FEV$_1$=forced expiratory volume in 1 s

Number of patients	10
Gender (females/males)	1/9
Age, yr (range)	66 (47–75)
Height, cm	172 (5)
Weight, kg	77 (9)
VC, litres	3.6 (0.9)
FEV$_1$, litres	2.5 (0.8)
FEV$_1$ (% of VC)	68 (10)

and 90%, were evaluated further. The measurements were performed under two different driving pressure (DP) settings (2.0 and 3.0 atm); all other variables, such as FI$_{O_2}$ (1.0), inspiration duration (50%) and frequency (100 cpm) remained unchanged. From the continuous P_{aw} tracings we measured peak inspiratory pressure (PIP) and end-expiratory pressure (EEP).

Changes of P_{aw} during progressive airway obstruction were analysed using nonparametric analysis of variance for repeated measurements (Friedman test) followed by paired Wilcoxon's signed rank tests with Bonferroni correction. Proximal and distal P_{aw} values without obstruction were compared using Wilcoxon's signed rank test. The level of significance was set at P=0.05. Continuous data are presented as mean (SD).

All patients had a pulse oximeter saturation of ≥90% throughout the procedure. No lung injury or surgical emphysema was noted up to 4 h after the intervention. Biometric and clinical data of the patients are summarized in Table 1.

During jet ventilation with a DP of 2.0 atm (Figure 2), gradual obstruction of the left mainstem bronchus resulted in a progressive increase of proximal PIP from 7.5 (2.6) to 9.5 (3.5) mm Hg (P=0.0008). In contrast, proximal EEP remained unaffected by airway obstruction (1.8 (2.6) and 1.9 (2.5) mm Hg). Without airway obstruction, there was no difference between distal and proximal PIP, or between distal and proximal EEP. Gradual airway narrowing did not affect distal PIP, but caused a highly significantly increase of distal EEP compared with the unobstructed airway lumen, from 2.5 (3.4) to 5.4 (3.6) mm Hg (P=0.0005). With a DP of 3.0 atm, these effects on P_{aw} were more pronounced: proximal PIP increased from 9.7 (3.7) to 13.0 (5.1) mm Hg (P=0.0001), proximal EEP decreased from 3.2 (2.9) to 1.8 (1.8) mm Hg (P=0.0001), distal PIP did not change and distal EEP increased significantly from 3.2 (3.6) to 8.0 (4.3) mm Hg (P<0.0001).

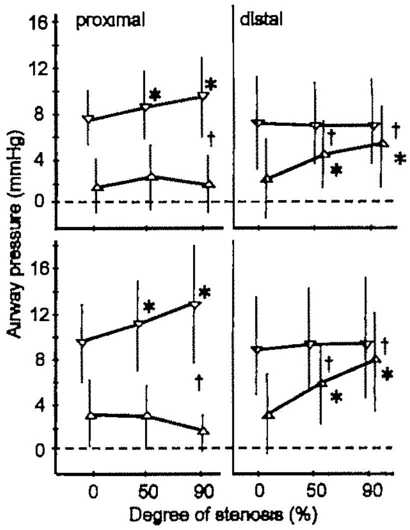

Fig 2 Proximal and distal P_{aw} during 0%, 50% and 90% obstruction of the airway and a driving pressure of 2.0 atm (upper segment) and 3.0 atm (lower segment) Values are expressed as mean±SD; *Significantly different from P_{aw} without obstruction (P<0.025), †Pressure amplitude significantly different from that without obstruction (P<0.025).

Comment

HFJV is a convenient method of ventilation for rigid bronchoscopy, but P_{aw} must be monitored continuously, especially if additional instruments are inserted into the bronchoscope. These devices may cause some airway obstruction: the recently introduced endosonography probe causes near complete airway obstruction.[4] We have shown that both PIP and EEP were affected by the degree of airway obstruction and by the applied DP: proximal PIP and distal EEP increased significantly, while proximal EEP and distal PIP remained unaffected. P_{aw} alterations were more pronounced with a DP of 3.0 atm than at 2.0 atm. Air trapping became significant when the obstruction occupied 50% of the original airway cross-sectional area. This corresponds to findings of Ayuso and colleagues, who found sufficient gas exchange with <50% of the cross-sectional area of the airway obstucted.[6]

The relevance of these findings for the routine application of HFJV during rigid bronchoscopy depends on factors such as jet flow, airway dimensions and degree of obstruction, and on the interaction between these factors. The increase in distal EEP during progressive airway obstruction may not necessarily be dangerous, since it was always less than the distal PIP observed without airway obstruction. The slight increase in proximal PIP is not likely to damage the lungs.

In summary, short-term near-total occlusion of the airway during jet ventilation beyond the tip of the rigid bronchoscope may slightly increase proximal peak P_{aw} and increase distal EEP. These effects depended on the degree of obstruction and the DP, but were never high enough to cause overinflation of the lung or even barotrauma. Nevertheless, careful and continuous monitoring of airway pressure (as used with modern jet ventilation equipment) and observation of the thoracic excursions during jet ventilation are indispensable during endoscopic instrumentation.

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Transcranial magnetic-evoked potentials under total intravenous anaesthesia and nitrous oxide

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Magnetic stimulation of the cortex and recording of the motor-evoked potentials (MEPs) by electromyography (EMG) is a well proven method to assess the descending pathways of the spinal cord and detect neurological impairment. We have assessed, in 33 adult patients undergoing spinal surgery, the influence of four total i.v. anaesthesia regimens (TIVA) on this recording technique. In 20 patients, the effect of 50% nitrous oxide was also studied. MEP amplitudes, latencies and success rates of stimulation were obtained in the steady-state after induction of anaesthesia. Combinations of midazolam and ketamine, and alfentanil and etomidate had the least effect on MEPs. Propofol (in combination with alfentanil or ketamine) showed marked depression of the MEP amplitude and the lowest success rates of stimulation. The latencies did not change at all. The addition of nitrous oxide significantly depressed the registered MEPs and lowered the success rates.

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Keywords: brain, electromyography; brain, evoked potentials; brain, cortex; anaesthesia, i.v.; anaesthetic gases, nitrous oxide

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Recording motor-evoked potentials (MEPs) is regarded as a sensitive method of monitoring the integrity of descending motor tracts of the spinal cord. Muscle action potentials of the upper or lower limbs are the responses to the central stimulation. Good correlation between neurological deficits and MEP changes have been shown in animal models and in humans.

Electrical stimulation may be used, but we prefer single-pulsed magnetic stimulation which is not painful. Previous studies have shown that the sensivity of MEPs is compromised by the suppressive action of many commonly used anaesthetics, but the results of human and animal studies are often conflicting. This study was designed to determine the effects of four i.v. anaesthesia techniques on MEPs recorded in patients undergoing spinal surgery.

Methods and results

The study was approved by the Ethics Commitee of the Ruhr University Bochum. It included 33 adult patients of both sexes, ASA class I–II, mean age 51 yr, mean body weight 77 kg, who were due to undergo surgery for lumbar disc hernia. Patients with a history of seizure, with implants or neuropathy were excluded. The patients were allocated randomly to one of four groups, according to the combination of i.v. anaesthetic drugs to be used: alfentanil–etomidate (AE); alfentanil–propofol (AP); propofol–ketamine (PK); midazolam–ketamine (MK).

Prior to the administration of any drug, baseline MEP recordings were obtained. All patients then received midazolam 0.05 mg kg^{-1} i.v. as premedication. Anaesthesia was induced by i.v. injection (lasting 30 s) of: in group AE, alfentanil 20 μg kg^{-1} and etomidate 0.3 mg kg^{-1}; in group AP, alfentanil 20 μg kg^{-1} and propofol 2 mg kg^{-1}; in group PK, propofol 2 mg kg^{-1} and ketamine 2 mg kg^{-1}; in group MK, midazolam 0.1 mg kg^{-1} and ketamine 2 mg kg^{-1}. Mask ventilation was started by a second anaesthetist at the first sign of unconsciousness or respiratory depression. Thereafter, a continuous i.v. infusion was started: in group AE, alfentanil 100 μg kg^{-1} h^{-1} and etomidate 0.6 mg kg^{-1} h^{-1}; in group AP, alfentanil 100 μg kg^{-1} h^{-1} and propofol 10 mg kg^{-1} h^{-1}; in group PK, propofol 10 mg kg^{-1} h^{-1} and ketamine 2 mg kg^{-1} h^{-1}; in group MK, midazolam 0.1 mg kg^{-1} h^{-1} and ketamine 2–4 mg kg^{-1} h^{-1}. Tracheal intubation was performed, facilitated by suxamethonium 1.5 mg kg^{-1} after precurarization with atracurium 5 mg. If necessary, additional doses of etomidate, propofol or ketamine were injected before intubation. Ventilation of the lungs was maintained with 40% oxygen in air for 15 min. At this point, anaesthesia was regarded as being in a steady-state and MEP measurements were again taken. There was no muscle relaxation. Oscillometric blood pressure, heart rate, oxygen saturation and end-tidal carbon dioxide were controlled for each series of measurements.

After the steady-state measurements, 50% nitrous oxide was added and maintained for 10 min after reaching the desired end-expiratory concentration (five patients from each group) and MEP recordings obtained. This completed the study and the patients underwent the operation with enflurane in nitrous oxide–oxygen for maintenance of anaesthesia.

For the recording of MEPs, central stimulation was performed with a magnetic stimulator (Magstim 200, The Magstim Co., Wales, UK), which produces a maximum magnetic field of 1.5 Tesla. A single coil (diameter 14 cm) was placed over the vertex. Its best position was determined in the awake state and marked on the scalp. The stimulations were started at 30% of maximum power. Thereafter, the power was increased in steps of 5% until a response was observed (the brain stimulation threshold). Electromyographic responses (EMG) to stimulation were recorded in duplicate from the contralateral thenar muscles using subdermal paired needle electrodes. A Neuropack Four (Nihon Kohden, Tokio, Japan) was used to record MEPs. Stimulation threshold, success rates, latency and amplitude of the magnetic motor-evoked potentials were determined.

For statistical evaluation, the Wilcoxon test for matched pairs and the Kruskall–Wallis test were used. A *P*-value of <0.05 was considered statistically significant.

The results are presented in Table 1. Each drug combination produced a significant increase in threshold stimulation, but the MEP amplitude was not depressed by midazolam and ketamine (MK), or by alfentanil and etomidate (AE). The observed increase in amplitude in the midazolam/ketamine group was not significant. Combinations using propofol led to a considerable and significant reduction in the MEP amplitude. The MEP latencies were unaffected by each combination. When considering the success rates of obtaining a response to stimulation, the combinations midazolam–ketamine and alfentanil–etomidate were superior to both combinations using propofol (AP and PK). The addition of nitrous oxide had a pronounced depressive effect on MEPs. All patients recovered well after surgery.

Comment

Serious neurological deficits with postoperative loss of motor function in the limbs can complicate neurosurgical, orthopaedic or abdominal vascular surgery procedures. Animal studies have suggested that magnetic motor-evoked potential (MEP) monitoring is more sensitive than somatosensory-evoked potential (SSEP) monitoring in detecting spinal cord injury.[1] Combined neuromonitoring, consisting of SSEP and MEP may be useful.

The results of our study demonstrate that MEPs were least affected in the AE and MK groups. Etomidate, together with fentanyl, has been shown to allow MEP recording even in patients with pre-existing spinal neuropathy with a success

Table 1 Changes in motor-evoked potential amplitude, latency, threshold, and arterial blood pressure and heart rate, after application of four i v anaesthesia regimens and nitrous oxide. Amplitude, latency and threshold· mean (SEM);mean arterial pressure (MAP) and heart rate (HR): mean (SD)

	Group AE **Alfentanil–etomidate (n=9)**			**Group AP** **Alfentanil–propofol (n=8)**		
	Before	**Steady-state**	***P*<0.05**	**Before**	**Steady-state**	***P*<0.05**
Amplitude (µV)	245 1 (86 3)	229.5 (111.6)		182 2 (35.5)	7.8 (7 8)	+
Latency (ms)	26.7 (1.1)	27.8 (1 0)		26.7 (0,7)	24.0	
Threshold (%)	51 7 (2.6)	95 6 (4.4)	+	51.9 (4.5)	100 (0)	+
Success rate		7/9=77 7%			1/8=12.5%	
MAP	108.6 (11.3)	84.8 (6.2)		101.7 (7.4)	91.3 (19 6	
HR	81.0 (8 9)	64.6 (6 6)		73 2 (7.8)	63.7 (6.5)	

	Group PK **Propofol–ketamine (n=8)**			**Group MK** **Midazolam–ketamine (n=8)**			**Effect of** **nitrous oxide**		
	Before	**Steady-state**	***P*<0.05**	**Before**	**Steady-state**	***P*<0.05**	**Before**	**After**	***P*<0.05**
Amplitude (µV)	300.1 (76.1)	72 4 (43.5)	+	265 4 (113.3)	525.5 (243 6)		345.6 (110.8)	1[illegible]2.5 (95.1)	+
Latency (ms)	25.5 (0.9)	25.2 (1.8)		25.0 (0.5)	25.5 (0 5)		26 2 (0.7)	2[illegible].0 (0 4)	
Threshold (%)	50.8 (2 8)	100 (0)	+	53.1 (2.8)	97 5 (2.5)	+	97.0 (2.1)	1[illegible]0 (0)	
Success rate		5/8=62.5%			7/8=87 5%			1[illegible]/20=55%	
MAP	101 3 (8.7)	93.4 (14.3)		109 1 (8 4)	112 6 (12.5)				
HR	69.0 (7.7)	66.2 (6.6)		77.1 (14 1)	80 2 (17 6)				

rate similar to the 77.7% of our AE group.[2] Induction doses of etomidate, however, can lead to significant depression of the MEPs.[3] In contrast to previous investigations on the effect of propofol on magnetically induced potentials in rats,[4] our studies clearly indicate that propofol significantly affects MEP recordings. A similar result was obtained by Taniguchi *et al.*[3] Ketamine seems to diminish the depressant effect of propofol when the alfentanil–propofol group is compared with the propofol–ketamine group, where propofol was applied in the same dosage. This might be due to a central excitatory effect, because ketamine, in a small dosage, was found to increase the MEP amplitude up to 120% from baseline.[5] It seems possible that in our studies, ketamine, combined with smaller doses of propofol, might have achieved better results. We could also show a strong depressant effect of nitrous oxide on MEPs. The success rate of obtaining a response was low (55%). Nitrous oxide, in a concentration of less than 50%, had previously been recommended, although a depressant action had also been reported.[6] None of our techniques affected the MEP latencies. In this study, MEP responses were recorded from intact motor pathways of the upper limbs. In the case of pre-existing neurological deficits and in the case of also monitoring the lower limbs, the results might have been slightly modified (e.g. with regard to the success rates), but certainly not completely different.

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Motor block during patient-controlled epidural analgesia with ropivacaine or ropivacaine/fentanyl after intrathecal bupivacaine for Caesarean section[†]

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We compared patient-controlled epidural analgesia (PCEA) with ropivacaine alone or combined with fentanyl in terms of analgesic efficacy, motor weakness and side-effects in patients who had received spinal anaesthesia for elective Caesarean section. ASA I patients received combined spinal–epidural anaesthesia and were randomly assigned, in a double-blind study, into two groups after operation: group R (n=23) received PCEA ropivacaine 0.1%, bolus 5 mg, lockout 15 min, 3 mg h^{-1} background infusion, and group RF (n=24) received PCEA 0.1% ropivacaine/fentanyl 2 $\mu g\ ml^{-1}$ at identical settings. Pain and satisfaction on a 100 mm visual analogue scale (VAS) and side-effects were noted. Incidence of motor weakness (Bromage grade 1 or higher) was 48% (11/23) at 8 h in group R compared with 13% (3/24) in group RF (P=0.025). Pain scores on movement were lower in group RF at 8 and 12 h and at rest at 6 and 8 h (P<0.05 for each comparison). Analgesic consumption was less in RF (P=0.041), but there was no difference in time to first request for supplementary analgesia. Patient satisfaction with post-operative analgesia (mean (SD)) was higher in RF (79 (23) *vs* 57 (29) mm, P=0.045). Caution should be exercised using ropivacaine PCEA after spinal bupivacaine for Caesarean section, because its reputed motor-sparing property may be unreliable.

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Keywords: anaesthetic techniques, epidural; analgesia, patient-controlled; anaesthetics, local, ropivacaine; anaesthetics, analgesics, opioid; anaesthesia, obstetrics

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Analgesic techniques for Caesarean section must be highly effective and yet allow early mobilization to enable these women to care for their babies. While patient-controlled epidural analgesia (PCEA) with local anaesthetics provides good analgesia, it causes motor weakness, limiting post-operative mobilization.[1] Ropivacaine, the most recent amide local anaesthetic introduced into clinical practice, reportedly produces less motor weakness than bupivacaine.[2] Ropivacaine epidural analgesia after spinal anaesthesia has not been reported. We compared PCEA ropivacaine alone or combined with fentanyl after Caesarean section under bupivacaine spinal anaesthesia, in terms of analgesic efficacy, motor weakness and side-effects.

Methods and results

After obtaining institutional ethics committee approval and written informed consent, 50 women scheduled for elective Caesarean section under regional anaesthesia were enrolled into the study. Excluded were patients other than ASA I, patients for whom a central neuraxial block was contra-indicated and those with a history of adverse reaction to any study medication. Patients were briefed preoperatively on visual analogue scales (VAS) and how to operate the PCEA.

After i.v. access had been established and an infusion of crystalloid commenced, all patients had a combined spinal–epidural (CSE) anaesthetic. The epidural space was identified at L2–3 or L3–4 using a loss of resistance to saline technique with the patient in a sitting position. Dural puncture was performed by a needle-through-needle technique with a Whitacre 26G needle; hyperbaric 0.5% bupivacaine 2.6 ml was injected into the intrathecal space. An epidural catheter was then inserted into the epidural space.

When surgery was complete, patients were randomized, by a sealed envelope technique, into one of two groups: group R (n=25) received PCEA 0.1% ropivacaine, bolus 5 mg, lockout 15 min, with 3 mg h^{-1} background infusion.

[†] Presented in part at the Anaesthetic Research Society Meeting, St George's Hospital, London, November 1998 and at the Obstetric Anaesthetists Association Annual Scientific Meeting, Liverpool, April, 1999.

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Group RF (n=25) received PCEA 0.1% ropivacaine/fentanyl 2 μg ml^{-1}, at identical settings to group R. The analgesic regimen was prepared by the anaesthetist managing the patient, who was not subsequently involved in data collection. It was commenced in the recovery room while the spinal block was still effective. Patients and nursing staff were blind to the group randomization.

Pain at rest and on movement (sitting forward) on a 100 mm VAS at 2, 4, 6, 8, 12 and 24 h, satisfaction with postoperative analgesia at 24 h (VAS) and the incidence of nausea and pruritus were recorded by the patients on a four-page individual patient diary. Dermatomal sensory level was noted using ethyl chloride spray at the commencement of the study and at 8 h. Motor block was evaluated using a modified Bromage scale by nursing staff who were familiar with these assessments. If patients had inadequate analgesia, supplementary rescue analgesia with oral codeine 30 mg/paracetamol 500 mg was available. Total PCEA consumption was noted.

Postoperative monitoring consisted of hourly respiratory rate, pulse rate and non-invasive blood pressure measurements for 4 h and thereafter at intervals of 4 h. Hypotension was defined as systolic blood pressure <90 mm Hg. Sedation was assessed on a four-point scale: 0=fully alert, 1=drowsy, eyes closed occasionally; 2=asleep but roused easily on speaking to the patient; 3=profoundly sedated, roused by physical stimulation.

Data were analysed in GraphPad Prism™, version 2.0. Physical characteristics and satisfaction scores were compared using the unpaired t-test. VAS pain and total analgesic consumption were compared using the Mann–Whitney U-test. Contingency tables were constructed for categorical data and analysed by χ^2 analysis with Yates' correction. The prospective study power calculation was based on analgesic data. Previous studies of women after Caesarean section indicated a standard deviation of the order of 30 mm in early postoperative pain scores. We took a VAS reduction of 25 mm to be clinically significant, hence 24 patients were required in each group to give an α value of 0.05 and a β value of 0.2.

Although 25 patients were enrolled in each group, only 23 in group R and 24 in group RF were deemed eligible for statistical analysis. One patient was withdrawn from each group because of technical difficulties with the epidural catheter. Another patient's data were lost from group R because of PCEA provider pump failure. A further two patients were withdrawn from the ropivacaine group at 12 h because of profound, prolonged motor block. They were included in the analysis as the only missing data were at 24 h.

The two groups did not differ in age, weight or parity. Patients receiving ropivacaine alone had significantly higher VAS pain scores at 6 and 8 h at rest and at 8 and 12 h on movement. Total analgesic consumption was less in the RF group than in group R and no patient in RF requested supplementary oral analgesia compared with eight patients in group R (P=0.005). There was no difference in the time to first request for supplementary analgesia. Patients in group RF had significantly higher scores for satisfaction with their postoperative analgesia compared with group R (P=0.045) (Table 1).

The incidence of demonstrable motor weakness (Bromage grade 1 or above) was significantly higher (P=0.025) in group R than in group RF at 8 h but not at 12 h. When patients with Bromage grades 2 or 3 were analysed separately, there was no statistical difference. No patient was allowed to walk if any motor weakness was detected. The two patients in group R who were withdrawn at 12 h had fully recovered by 24 h. There was no difference between the groups in sensory level at 8 h. Pruritus was significantly more likely in group RF than in group R (P=0.033), but no patient requested treatment. There were no differences in the incidences of nausea, hypotension or sedation between the groups (Table 1).

Comment

This is the first report, to our knowledge, of epidural ropivacaine for continuing postoperative analgesia after spinal anaesthesia. The increasing use of CSE techniques increases the possibility of epidural administration of ropivacaine after spinal anaesthesia with bupivacaine. The principal finding is the unexpectedly high incidence and duration of motor block observed in patients receiving PCEA with ropivacaine. This observation differs from the initial clinical impression of ropivacaine, which suggested a motor-sparing effect.[2] However, a study of PCEA epidural 0.125% ropivacaine compared with 0.125% bupivacaine in labour found that they were clinically indistinguishable in terms of motor weakness.[3]

We chose a background infusion of ropivacaine 0.1%, believing that it would provide an acceptable balance between adequate analgesia and minimal motor block. In retrospect however, it is clear that we failed in this objective because we underestimated the pain produced by Caesarean section in our patients. In a randomized, double-blind study of three solutions of ropivacaine/fentanyl for PCEA after lower abdominal surgery, 0.05% ropivacaine/fentanyl 1 μg ml^{-1} produced equivalent analgesia to 0.2% ropivacaine/fentanyl 4 μg ml^{-1}. However, the latter group had a 30% incidence of motor block, compared with none in those receiving the lower concentration of ropivacaine.[4] Our choice of ropivacaine 0.1% could reasonably have been expected not to aggravate motor weakness. Moreover, recent work has shown that the relative potency of ropivacaine compared with bupivacaine is only 0.6 and the EC$_{50}$ for the minimum local anaesthetic concentration for ropivacaine in labour is approximately 0.16%.[5] Hence, 0.1% ropivacaine should have been even less likely to produce motor block than 0.1% bupivacaine.

Although the difference is statistically significant only when patients with all grades of motor weakness are included, this unexpected finding is clinically important because even Bromage grade 1 weakness precludes

Table 1 Physical characteristics, analgesia, motor weakness and side-effects. All data are expressed as mean (SD) or median (interquartile range) except where stated

	Ropivacaine (*n*=23)	**Ropivacaine/fentanyl** (*n*=24)	**Statistical significance**
Age (yr)	32.4 (5.5)	28 5 (5.0)	n.s.
Weight (kg)	80.4 (8 3)	82.0 (11 2)	n.s.
Parity	1 (0–3)	1 (1–3)	n s
Total PCEA ropivacaine consumption in 24 h (mg)	199 (23)	175 (15)	*P*=0.041
Supplementary oral analgesia, *n* (%)	8 (35%)	0 (0%)	*P*=0.005
Time to supplementary analgesia (h)	9.7 (2 7)	6 6 (2.4)	n.s.
Pain VAS at rest, 6 h (mm)	20 (13–40)	8 (1–25)	*P*=0.039
Pain VAS at rest, 8 h (mm)	24 (19–35)	12 (2–5)	*P*=0 047
Pain VAS on movement, 8 h (mm)	54 (34–60)	35 (4–35)	*P*=0 045
Pain VAS on movement, 12 h (mm)	53 (30–70)	39 (20–55)	*P*=0 049
Patient satisfaction VAS (mm)	57 (29)	79 (23)	*P*=0.045
Motor weakness at 8 h, *n* (%)	11 (48%)	3 (13%)	*P*=0.025
Bromage score=1	6 (26%)	2 (8%)	n s.
Bromage score=2	3 (13%)	1 (5%)0	n s
Bromage score=3	2 (9%)		n.s
Motor weakness at 12 h, *n* (%)	6 (26%)	2 (8%)	n.s.
Bromage score=1	4 (17%)	2 (8%)	n s
Bromage score=2	0	0	n.s.
Bromage score=3	2 (9%)	0	n.s.
Sensory level at baseline	T5 (T4–T10)	T6 (T3–T10)	n s.
Sensory level at 8 h	T11 (T10–L2)	T10 (T8–L1)	n s.
Pruritus, *n*	3	11	*P*=0.033
Hypotension, *n*	2	2	n.s
Nausea, *n*	1	3	n.s.
Sedation score >1, *n*	0	2	n.s.

ambulation. Inadvertent intrathecal spread of ropivacaine (via the small dural hole created by the spinal component of the CSE) could possibly explain our observations, although there was no suggestion of dural puncture in any of our patients. Indeed, it has been shown that dural puncture with a 26 gauge Whitacre spinal needle before epidural injection (as in the present study) increases the caudal, but not the cranial, spread of epidural local anaesthetics.[6]

It is also possible that low thoracic placement of the epidural catheter may have been more appropriate. Repeated introduction of boluses of local anaesthetic into the lumbar area may not provide analgesia in the lower thoracic dermatomes, yet accumulation may increase the risk of motor weakness in the lumbar dermatomes. Although there is also greater sensitivity of neural tissue to local anaesthetics during the later stages of pregnancy, this is an unlikely explanation because patients in group RF did not have as much leg weakness as those in group R. However, it is noteworthy that patients in group R received a significantly higher dose of ropivacaine than patients in group RF over the duration of the study, presumably because their analgesia was less satisfactory than in group RF.

An alternative explanation is an interaction between the two local anaesthetics. An experimental model of profound nerve block under spinal anaesthesia found that combinations of amide local anaesthetics could produce unpredictable prolongation of the block. Although the mechanism is unclear, these investigators postulated that local anaesthetics could interact at the sodium channel to prolong effective duration.[7] Whether this effect could be more pronounced on motor as opposed to sensory nerves is unknown.

In conclusion, we found a higher incidence of motor weakness after 8 h in patients receiving PCEA ropivacaine compared with a ropivacaine/fentanyl mixture after bupivacaine spinal anaesthesia. The reason for this finding is unclear, but further studies are indicated to clarify the optimum dose regimen of epidural ropivacaine and fentanyl after spinal anaesthesia. In the interim, caution should be exercised when administering epidural ropivacaine after bupivacaine spinal anaesthesia.

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BJA

CASE REPORTS

Repetitive synchronized cyclical oscillations of multisystem parameters subsequent to high-dose thiopental therapy for status epilepticus secondary to herpes encephalitis

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We report a case of status epilepticus secondary to herpes encephalitis, treated with thiopental infusion and mechanical ventilation. The computerized storage and analysis of physiological data led to the detection of repetitive synchronized cyclical oscillations of arterial pressure, heart rate, EEG parameters, peripheral temperature and core temperature. Arterial pressure oscillations have been described in patients who are severely systemically unwell; cardiovascular and brain electrical activity may also oscillate in the presence of raised intracranial pressure. In contrast, this patient had no features of severe systemic illness or of raised intracranial pressure. Our hypothesis is that high-dose thiopental may have been a cause of our findings by producing autonomic dysfunction.

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Case report

An 18-yr-old male with no history of epilepsy was treated in the emergency unit for status epilepticus. There were no focal neurological signs or evidence of raised intracranial pressure. Seizure activity persisted despite cumulative total doses of phenytoin 1500 mg and diazepam 60 mg. A loading dose of thiopental 1000 mg was therefore given followed by tracheal intubation and mechanical ventilation. Positive herpes zoster antibody serology and cerebrospinal fluid polymerase chain reaction studies later confirmed the diagnosis of viral encephalitis.

On admission to the intensive care unit (ICU), intermittent positive-pressure ventilation was continued, together with a thiopental infusion titrated up to 500 mg h^{-1} under the guidance of a continuously running paper electroencephalogram (EEG), which confirmed the presence of burst suppression and the absence of seizure activity. Standard monitoring included continuous electrocardiography (ECG), invasive arterial pressure, capnography, respiratory flow/volume measurements, hourly urine output measurements and repeated arterial blood gas analysis. The cardiorespiratory, haematological, hepatic, renal, biochemical and blood gas profiles were within normal limits. In particular, no signs of poor tissue oxygenation or pH imbalance were observed. Cranial CT and MRI scans showed no abnormalities. Additional therapy included acyclovir 750 mg 8-hourly and a crystalloid infusion at 100–250 ml h^{-1}. No sympathomimetic therapy was required. No subsequent seizures were detected clinically or electroencephalographically, and the thiopental infusion was stopped on day 2, by which time the patient had received 7975 mg over 20 h. Regular intravenous phenytoin therapy (250 mg 12-hourly) was continued.

On day 3, with the relatives' assent and research ethics committee approval, specialized monitoring was set up as part of the EU Biomed 1 IMPROVE intensive care project[1] in order to establish an annotated data library. This involved acquiring and storing continuous physiological variables (including arterial pressure, ECG and capnographs at sampling rates between 25 and 100 Hz) and intermittent annotations (exact timing of drug doses, insertion of lines and any other interventions). This period of specialized

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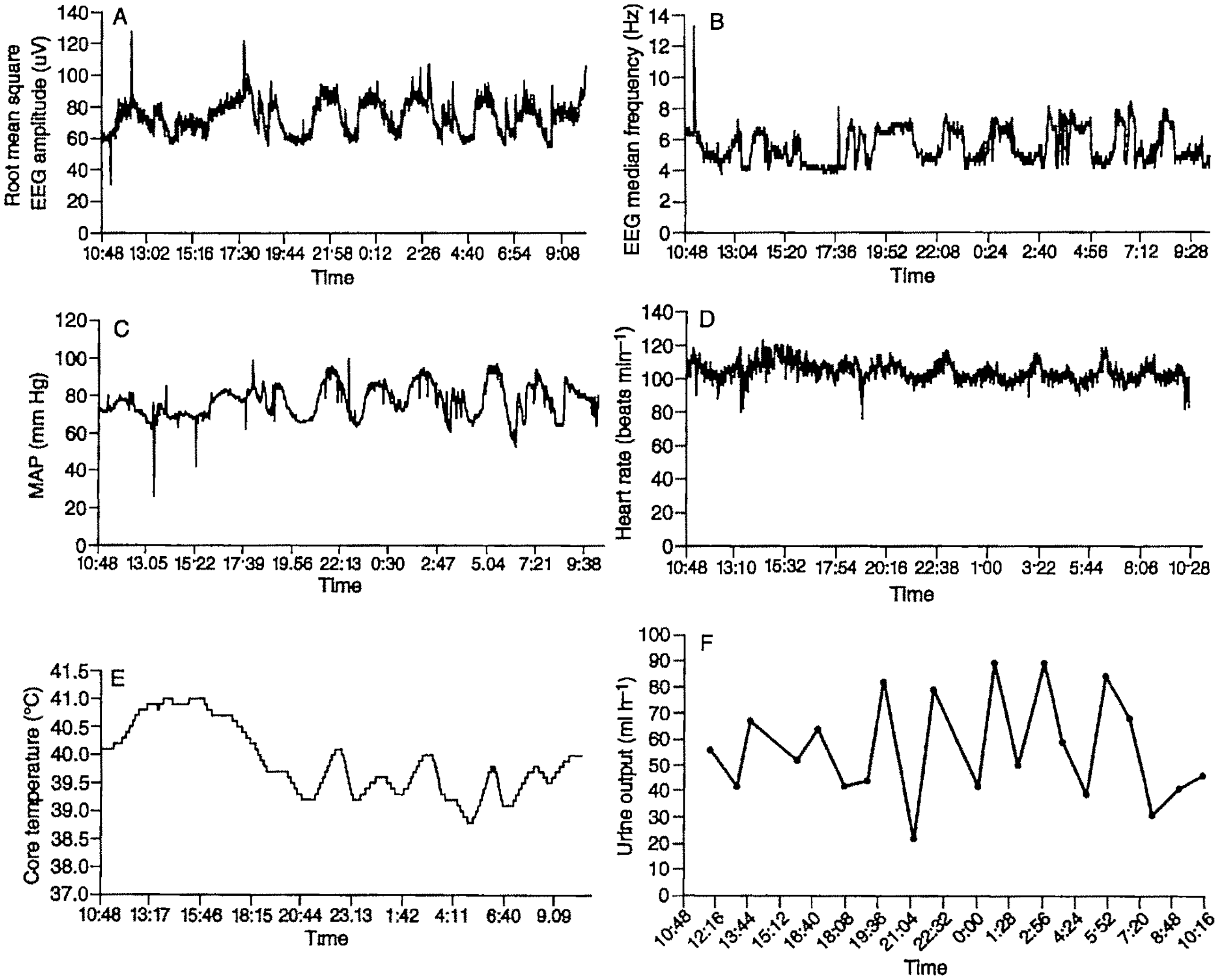

Fig 1 Twenty-four-hour display of polygraphic physiological measurements. The variables are shown on separate graphs for clarity (A) Root mean square EEG amplitude, a frequently used processing technique in which digitized values for EEG amplitude are individually squared within a sampled period; subsequently the mean is extracted and the square root of the mean is taken. (B) EEG median power frequency, the frequency at which half the spectral power is above and half is below within a sampled period. (C) Mean arterial pressure (D) Heart rate (E) Core temperature. (F) Urine output.

monitoring lasted 24 h, during which time continuous digitized EEG was also recorded.[2] No notable clinical events occurred in this 24 h period, and biochemical and blood gas profiles remained within normal limits. As on admission, there were no signs of raised intracranial pressure.

Subsequently, the patient made an uncomplicated recovery; his level of consciousness improved and the tracheal tube was removed on day 6. At this point his Glasgow Coma Scale score was 15 and gross intellectual functions were normal. He left the ICU on day 7 and went home on day 14.

Retrospective trend analysis revealed marked cyclical oscillations of the multisystem physiological variables over 24 h (Fig. 1). Assessments were made of raw data (peripheral and core temperature, mean arterial pressure, heart rate) and frequently used processed EEG parameters. The latter consisted of root mean squared amplitude (each EEG amplitude digital value within a sampling period is squared, a mean is subsequently taken and the square root of this is taken) and median power frequency (frequency at which half the spectral power is above and half is below). Peaks of relative hypertension occurred synchronously with peaks in EEG amplitude. Oscillations in heart rate and EEG frequency both showed a close inverse relationship to arterial pressure and EEG amplitude. Peripheral temperature and urine output also showed oscillations, though these did not show exact synchrony with the other parameters.

Discussion

The variability of physiological parameters is an important indicator used in assessment and prediction in intensive care patients. Several types of variability have been observed: the simplest example is the ECG R–R interval, which is a good measure of (i) reactivity to stress during critical illness and (ii) autonomic neuropathy. Similarly, EEG reactivity to stimuli carries the same implications; the presence of reactivity is reassuring, and the lack of reactivity (in the absence of drug-induced or hypothermic coma) suggests a poor prognosis.[3]

More orderly variations exist in both cardiac and neurological signals. First-, second-, third- and, more recently, fourth-order blood-pressure waves have been described and summarized elegantly by Seiver and colleagues.[4] First- and second-order waves are descriptions of blood-pressure variations with each systolic beat and respiratory cycle, respectively. Third-order waves, with a cycle of 10–160 s, are a consequence of disordered autonomic feedback. Fourth-order waves (cycles of minutes to hours, as seen in this case) have been thought to be due to poor oxygen delivery to the tissues and are associated with a poor prognosis.[4 5] Electroencephalographers have described cyclical changes in association with sleep patterns;[6] the presence or absence of these features has, in turn, relevance to prognostication in coma.[7 8] Repetitive waves with cycling of minutes to hours are also seen in the EEG monitoring of patients with brain insult as a consequence of raised intracranial pressure.[9]

In this case, we considered three possible causes of the multiparameter oscillations. Classical fourth-order changes seemed unlikely, as severe systemic dysfunction was not evident. Covertly raised intracranial pressure may have been an alternative cause, though there was never any clinical or radiological evidence of it, or of persisting brain injury. Lastly, we could not exclude high-dose thiopental infusion as an important cause. Plasma levels were not measured, as these findings became apparent only on trend analysis after the cessation of monitoring. Our hypothesis is that high-dose thiopental may cause autonomic dysfunction, leading to loss of 'randomicity'; this would be similar to the hypothesis of fourth-order oscillations caused by poor tissue oxygen delivery in ill patients.

The interesting phenomenon of synchronized cyclical oscillations of physiological parameters should not automatically instil concern, and may prove to be a recognized finding when high-dose thiopental infusion is used or there is covert brain dysfunction. This may, in time, be clarified with the increasing sophistication of polygraphic trend analysis in intensive care, without which our findings would not have been apparent. To validate these findings, prospective studies of high-dose thiopental infusions (including the simultaneous measurement of plasma levels) and intracranial pressure monitoring should be encouraged.

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Loss of consciousness following spinal anaesthesia for Caesarean section

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A healthy parturient under spinal anaesthesia for Caesarean section lost consciousness for an hour, 20 min after the intrathecal injection of 2 ml of 0.5% heavy bupivacaine. The patient was haemodynamically stable before losing consciousness. The differential diagnosis is discussed.

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Spinal anaesthesia is increasingly used for Caesarean section[1] as it is remarkably safe and effective.[2] Its safety[3] lies in the fact that parturients are conscious throughout anaesthesia and are not exposed to the hazards of intubation. Patients can lose consciousness in the presence of a total spinal block,[4] usually characterized by severe hypotension.[5] However, loss of consciousness with this technique in a haemodynamically stable patient is unusual. We report a parturient who lost consciousness 20 min after a successful spinal anaesthetic block.

Case report

The parturient, a 25 yr old, 160 cm, 55 kg normotensive primigravida with mild polyhydramnios, required an elective Caesarean section for delivery of a baby with bilateral pleural effusions of unknown cause. She had no other medical condition of note; in particular, she had no psychiatric history. Plasma electrolytes were normal before surgery. Sodium citrate and oral ranitidine were given in the ward before delivery; no other drugs were administered and the patient was not on any medication. Immediately before spinal blockade, Unasyn 1.5 g (subactam 500 mg and ampicillin 1000 mg) diluted in sterile water was administered as an intravenous infusion. For spinal block, a 26 G Atraucan (B Braun) spinal needle was used at L3/4 in the midline with the patient in the sitting position. Cerebrospinal fluid flowed from the needle after a single attempt and 2 ml of 0.5% heavy bupivacaine was injected after initial aspiration. The patient was then placed horizontally with a left lateral tilt and a single pillow to support the head. A T4 level of block was obtained by 5 min and the Bromage score before surgery was zero. Before delivery of the baby, the parturient's arterial pressure was measured every 5 min with a Dinamap. This averaged around 110/60 mm Hg with one transient episode of hypotension (90/50 mm Hg) about 5 min after the spinal injection, which improved with the administration of ephedrine 5 mg. The heart rate averaged 80–100 beats min^{-1}. Three litres of oxygen were administered by nasal prongs; oxygen saturation was 99–100%. Hartmann's solution (500 ml) was given as a preload and a second 500 ml was commenced before the baby was delivered. During this period the patient was alert and communicating with the anaesthetist. No other drugs were administered for 15 min before delivery of the baby.

At the time of delivery, 20 min after administration of the intrathecal drug, the patient suddenly stopped communicating, as if going off to sleep. She was not responding to verbal commands or to deep pain. There was no frothing, and no uprolling of the eyeballs. The incident was not preceded by nausea and vomiting. There were no complaints of chest pain, inability to breathe or weakness of the upper limbs immediately before loss of consciousness. There was a transient period of apnoea with a dramatic drop in oxygen saturation to around 75%. The patient's lungs were ventilated with a face mask for 1 min on the circle system after which spontaneous ventilation resumed. No bronchospasm or urticaria was noted. The anaesthetist tried to intubate the patient at this stage but was unsuccessful as the patient had a very strong gag reflex. A decision was made not to give additional drugs to sedate or paralyse the patient as it was noted that she was able to protect her airway. Both of her pupils were about 3 mm wide and reactive to light. Throughout this period of loss of consciousness, arterial pressure averaged around 100/55 mm Hg and the pulse rate was about 80 min^{-1}. Ten minutes into the incident the patient was responding to deep pain

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with non-purposeful movements of the upper limbs. Gradually the movements on deep pain became more purposeful but there was still no verbal response. One hour after the onset of the incident, the patient opened her eyes to commands and had slurred speech when she attempted to talk. Muscle power in the upper limbs at this stage was grade 4 and her sensory level was at T2 bilaterally. The blood sugar concentration was 3.9 mmol litre^{-1}. One and a half hours after the onset of the loss of consciousness, the patient was fully alert and her upper limb muscle power was grade 5 with a sensory level at T5. When questioned about her loss of consciousness, she said that she had felt extremely sleepy, had gone to sleep and was unable to recall the event. Four hours after loss of consciousness, the spinal block had totally worn off, with grade 5 muscle power in all four limbs. The patient was discharged back to the ward where the anaesthetist visited her for the next few days. The baby died because of severe heart failure, with a single atrium, single ventricle and pulmonary atresia, 2 h after delivery.

Twenty-four hours after spinal injection, the patient complained of giddiness and a postural frontal headache which gradually worsened. CT scan results were normal and an EEG showed no abnormal foci. An epidural blood patch relieved the headache immediately. The patient was discharged 1 week after the incident with no further complaints.

Discussion

A non-sedated parturient given an intrathecal local anaesthetic injection should never lose consciousness. In this particular parturient, there was no history of epilepsy or diabetes to cause loss of consciousness. A blood sugar concentration of 3.9 mmol litre^{-1} is at the low end of the normal range but was not low enough to account for the loss of consciousness. The normal EEG indicated that the event could not be explained by an epileptic seizure. A CT scan done when the patient developed a headache 24 h after the incident was normal. This indicated that there was no space-occupying lesion intracranially to account for the loss of consciousness during the Caesarean section. As magnetic resonance imaging (MRI) is superior to CT scanning for evaluating most suspected central nervous system pathology,[6] we should, in retrospect, have subjected the patient to MRI instead. Only 2 ml of 0.5% bupivacine was given intrathecally and the patient was subsequently placed horizontally, so the signs could not be attributed to a total spinal block. The patient did not develop significant hypotension, respiratory depression or pupillary dilation to warrant a diagnosis of total spinal block.[4 5] The anaesthetist was certain that the loss of consciousness could not be attributed to any intravenous sedative drugs being given inadvertently, as no drugs were administered for 15 min before delivery of the baby. It was unlikely that the patient had an amniotic fluid embolism,[7] although the event occurred at the time of delivery of the baby. She was stable cardiovascularly and at no time was there any coagulopathy. The event was also unlikely to be the result of a pulmonary embolism,[8] as the patient had a normal cardiac rhythm. There was no cardiovascular compromise at the time of the event and no residual neurological deficit after regaining consciousness. However, echocardiography was not attempted. Air embolism occurring at the time of delivery can also be responsible for the loss of consciousness. For loss of consciousness to have occurred, air must have reached the left side of the heart through a patent foramen ovale. This was not ruled out by echocardiography, but air embolism is unlikely as there were no complaints of dyspnoea or chest pain,[9] nor was there residual neurological deficit beyond the period of loss of consciousness. The patient described by Davis, Glover and Maycock,[10] with cerebral arterial air embolism, not only had a prolonged recovery from general anaesthesia but had a neurological deficit for several days despite hyperbaric oxygen therapy.

Skowronski and Rigg[11] and Philip and Walter[12] described loss of consciousness in patients following the administration of epidural anaesthesia for labour. In both these parturients, the loss of consciousness had occurred, as in our patient, in the presence of remarkable haemodynamic stability. These were described as total spinal anaesthesia. These complications were probably the result of subdural spread. The signs that alerted the anaesthetists to the cranial extension in these case reports were difficulty in breathing,[11] arm weakness[12] and dysarthria.[12] These signs developed slowly with time and the anaesthetists involved were able to detect them. In our case, the loss of consciousness after 20 min of relatively uneventful spinal blockade was the first sign of a possible cranial extension. The loss of consciousness precluded detailed sensory and motor testing in the head, but the gradual and progressive return of function indicated that it could have been compatible with anaesthetic blockade that receded with time. Although we do not have radiological evidence to prove that this incident was caused by subdural blockade, we believe that the clinical events that occurred in our patient are in keeping with this suggestion.[5 13] These include relatively stable arterial pressure, slow onset of symptoms after 20 min and complete recovery after almost 2 h. The absence of sympathetic blockade[14 15] is consistent with subdural blockade.

The parturient could have lost consciousness as a psychogenic response to distress felt at the time of the Caesarean section, knowing that her newborn was critically ill and not expected to survive the neonatal period. Hysteria cannot be excluded from the differential diagnosis since measurements taken during the incident were normal except for a transient episode of hypoxia and the 1 h loss of consciousness. Normal antenatal and postnatal mental health makes this diagnosis improbable.

In summary, we have described loss of consciousness in a parturient who had a successful spinal block. The loss of consciousness occurred in the presence of remarkable haemodynamic stability. Despite investigations, we were unable to determine the cause. We can only speculate that a subdural block complicating the spinal block may have accounted for this most unusual event.

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Traumatic bilateral internal carotid artery dissection following airbag deployment in a patient with fibromuscular dysplasia

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This case describes a 39-yr-old male, presenting with left hemiplegia after a road traffic accident involving frontal deceleration and airbag deployment. Brain computerized tomography (CT) scan revealed a right parietal lobe infarct. Contrast angiography demonstrated bilateral internal carotid artery dissection and fibromuscular dysplasia. The patient was treated with systemic heparinization. Neurological improvement, evidenced by full return of touch sensation, proprioception and nociception began 10 days after the injury. To our knowledge, this is the first case report of carotid artery dissection associated with airbag deployment. Forced neck extension in such settings may result in carotid artery dissection because of shear force injury at the junction of the extracranial and intrapetrous segments of the vessel. Clinicians should consider carotid artery injury when deterioration in neurological status occurs after airbag deployment. We propose that the risk of carotid artery dissection was increased by the presence of fibromuscular dysplasia.

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Airbags were developed to decrease the incidence of death and severe injury following road traffic accidents.[1] Airbags are reported to cause injuries in 43% of deployments. The majority of these are minor (abrasions and contusions), but severe injury such as upper limb fracture occurs in 4% of cases.[1] This case report describes bilateral internal carotid artery dissection, associated with airbag deployment, in a patient with fibromuscular dysplasia.

Case report

A 39-yr-old male driver, height 165 cm, was involved in an acute deceleration, frontal-impact collision. He was restrained by both a seatbelt and an airbag. He was transferred by road ambulance to the Accident & Emergency unit at our institution. On initial examination the patient was haemodynamically stable. His Glasgow Coma Score (GCS) was 10/15 at the time of initial assessment but improved to 13/15 thereafter. Neurological examination revealed a left homonymous hemianopia, left hemiplegia and an upper motor neurone left 7th nerve palsy. Other injuries sustained included metatarsal fractures and anterior neck abrasions. Standard haematological and biochemical investigations and chest and cervical spine radiographs were normal. A brain computerized tomography (CT) scan showed a right parietal lobe infarct.

The patient was transferred to the neurosurgical intensive care unit for invasive arterial pressure monitoring and neurological observations. Supplemental oxygen was administered by facemask. Aspirin 300 mg once daily by mouth was prescribed for its antiplatelet effect. A second brain CT on hospital day 2 demonstrated haemorrhagic transformation of the right parietal lobe infarct. Duplex scan and magnetic resonance angiogram of the carotid arteries was inconclusive. Contrast angiography revealed bilateral internal carotid artery dissection, fibromuscular dysplasia of the internal carotid arteries and thrombus in the right internal carotid artery (Fig. 1). Heparin was commenced with a target activated partial thromboplastin time of 60 s. Warfarin was commenced with a target prothrombin time of 26 s.

Recovery of neurological function began with the return of normal GCS on hospital day 3. By day 10, touch sensation, proprioception and nociception in the left upper and lower limbs were evident. Left lower limb power had improved to grade 3/5 on day 24. However, the left faciobrachial palsy persisted. The patient was transferred to a rehabilitation hospital on day 26.

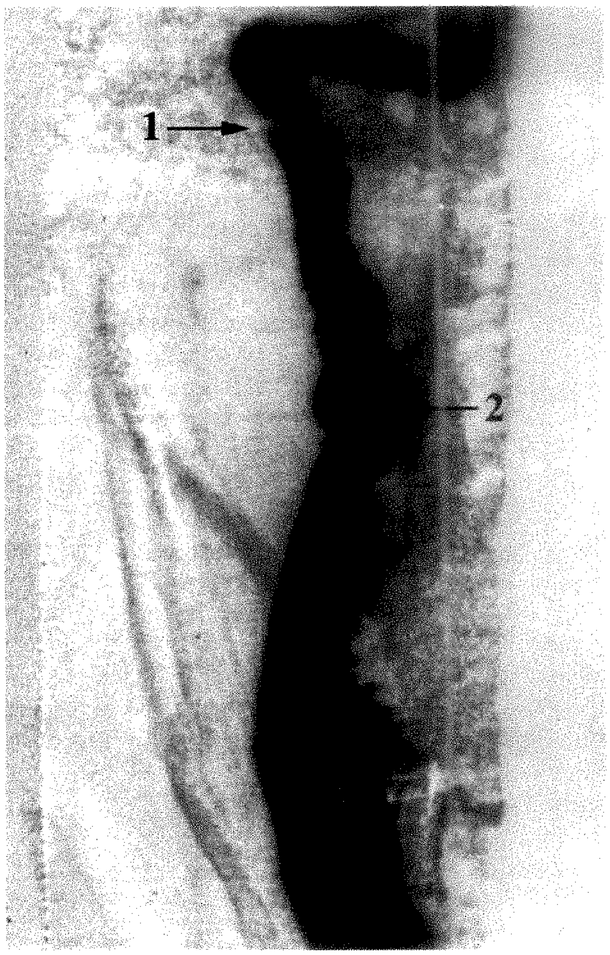

Fig 1 Right carotid angiogram showing intimal dissection (1) at the junction of the extracranial and intrapetrous segments of the internal carotid artery, and the 'string of beads' appearance (2) that is characteristic of fibromuscular dysplasia.

Discussion

Blunt carotid injury presents typically with neck abrasions and neurological sequelae, including hemiplegia, low GCS and a co-existing Horner's syndrome when the sympathetic chain is stretched across the transverse process of the first cervical vertebrae.[2,3] Road traffic accidents are the most frequent cause of blunt carotid injury.[3] The mechanism of injury to the internal carotid artery is thought to be a shear force applied to the vessel during forced neck extension, causing intimal dissection at the junction of the immobile intracranial and relatively mobile extracranial portions of the internal carotid artery.[2]

Fibromuscular dysplasia is an arterial developmental abnormality of unknown aetiology affecting medium-sized arteries.[4,5] The incidence of the disorder based on a series of 20 244 post-mortems is two per 1000 population.[4] There are four known subtypes, each with its own unique histological appearance (intimal fibroplasia, medial fibroplasia, medial hyperplasia and perimedial dysplasia).[5] Affected vessels are elongated, kinked and punctuated with stenoses and microaneurysms.[5] These abnormalities produce unique angiographic features which radiologists call the 'string of beads' appearance (Fig. 1). The presence of fibromuscular dysplasia may compromise the structural integrity of the affected vessels, including the carotid artery, and therefore predispose to vessel dissection after traumatic injury.

Patients with fibromuscular dysplasia are asymptomatic until they sustain a vessel dissection. They then present with ischaemia of the organs supplied by the affected vessel, for example cerebrovascular accident. Fibromuscular dysplasia is found in 15% of cases of spontaneous carotid dissection.[2 6] A report of bilateral internal carotid and vertebral artery dissection in a patient with fibromuscular dysplasia after a road traffic accident has been described.[7] Arteriography is the gold standard diagnostic test for both fibromuscular dysplasia and blunt carotid injury.[5 8]

The management of carotid artery dissection is controversial. Heparinization was associated with an improved outcome in the largest series of blunt carotid injuries.[3] However, the safety and efficacy of anticoagulation in the management of stroke following carotid injury has not been demonstrated.[9] In our patient, the apparent benefit of heparinization had to be balanced against the risks of a worsening stroke.

Airbag usage is increasing worldwide and is now mandatory in new cars in some countries.[1] Airbags function by preventing traumatic impact between the vehicle occupant and the vehicle interior. During a road traffic accident, sensors in the vehicle body detect deceleration and trigger airbag deployment.[1] To protect against injury, airbags must be fully expanded before the vehicle occupant is propelled forward by the deceleration of the accident. An airbag expansion speed of 200 mph is necessary. This rapid forceful expansion causes airbag-associated injury in 43% of deployments. In addition, fatal rupture of the ventral ligaments of the cervical spine and brain stem has been described secondary to forced neck extension.[10]

An increase in the incidence of airbag-associated injury is predicted.[1] Drivers of short stature, as in this case, are at increased risk of these injuries.[8 9] Their short stature makes it necessary to move the vehicle seat forward in order to reach the foot pedals, thereby bringing the upper body into the path of the expanding airbag. In the USA it is now recommended that airbags should be decommissioned if drivers cannot keep a wheel–chest distance of 10 inches.[1]

The evidence for airbag-mediated blunt carotid injury by means of forced neck extension is compelling in this case. A less likely explanation is that the patient initially sustained spontaneous carotid artery dissection because of fibromuscular dysplasia and then crashed. However, spontaneous dissections of the carotid artery typically present initially with minor clinical manifestations (e.g. headache),[10] and only develop neurological signs after several days.[11 12]

In summary, this is the first case report of bilateral internal carotid artery dissection, in a patient with fibromuscular dysplasia, associated with airbag deployment. The report suggests that clinicians should consider the possibility of carotid injury when neurological deterioration occurs after a road traffic accident with airbag deployment. Associated conditions, such as fibromuscular dysplasia, may increase the risk of carotid artery injury in this setting. Early carotid angiography is warranted to make the diagnosis.

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Anaesthetic management of a pregnant patient in a persistent vegetative state

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Pregnancy in a patient in a persistent vegetative state presents challenging therapeutic questions about the level of supportive management required, the assessment of fetal well-being, the timing and mode of delivery and the anaesthetic management of labour and delivery. We report the case of a 29-yr-old woman who had a favourable fetal outcome despite suffering hypoxic brain damage after a suicide attempt by a drug overdose. She was managed until the onset of labour on an intensive care unit and had a spontaneous vaginal delivery assisted by epidural anaesthesia.

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The term persistent vegetative state (PVS) describes a state of continuing 'wakefulness without awareness' that is usually due to a severe brain insult from a variety of possible causes.[1] PVS involves damage to the central nervous system, other systems being essentially normal. A pregnancy may be viable, creating an unusual scenario requiring difficult clinical and ethical decisions. In this report, we discuss the anaesthetic and intensive care management of a 29-yr-old patient who suffered hypoxic brain injury after a failed suicide attempt at 12 weeks gestation.

Case report

A 29-yr-old lady was 12 weeks pregnant with her second pregnancy. She had a history of depressive illness. There was also a history of marital discord. While abroad with her family, she attempted suicide and overdosed on a cocktail of antihypertensives (which belonged to her father-in-law), anxiolytics and antidepressants. The patient was found unconscious, and after admission to an intensive care unit (ICU) a computer tomographic (CT) scan of her brain showed gross ischaemic changes in the cerebral cortex consistent with severe hypoxic brain damage.

After air transfer to our ICU, 4 weeks after the suicide attempt, she had a Glasgow Coma Score (GCS) of 7 (spontaneous eye opening, no verbal response and an extensor response to pain). She responded to distressing situations by becoming increasingly agitated, sweaty and tachypnoeic. A tracheostomy had been performed at the referring hospital. The tracheostomy tube was changed to a fenestrated type to facilitate spontaneous ventilation, an enterostomy feeding tube was sited and a central venous catheter (CVP) was inserted to aid fluid management. She was treated for multiple respiratory, urinary and gastrointestinal infections with appropriate antibiotics, but continued to demonstrate intermittent pyrexia and persistent tachycardia.

A fetal ultrasound scan showed that the fetus was intact and small for date at 16 weeks, but did not appear to have any anatomical abnormality. A plan to manage the pregnancy expectantly was made. This involved weekly clinical assessment supplemented by regular ultrasound assessment of fetal growth. liquor volume and umbilical artery waveforms. In the absence of fetal or maternal indications, a requirement for early delivery or Caesarean section was not anticipated. These findings were discussed extensively with the family, who were particularly concerned about fetal survival. Arrangements were made initially to transfer the patient to a rehabilitation unit once her condition had stabilized. However, this decision was reversed after careful consideration of the risks to the patient and the fetus. She therefore remained in the ICU until delivery Whilst in the ICU she required substantial nursing care, although she was not artificially ventilated.

The ICU nursing staff were instructed in the palpation of uterine contractions and encouraged to request midwifery support if in doubt. At 35 weeks gestation, the patient developed regular uterine contractions, which seemed to be

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causing considerable distress. A lumbar epidural catheter was sited in the lateral position and an infusion of 0.25% bupivacaine commenced at a rate of 6–10 ml h^{-1}, which was adjusted according to the patient's agitation and the cardiovascular parameters. She was transferred to the delivery suite after spontaneous rupture of the membranes occurred. Continuous fetal heart rate monitoring identified a baseline rate of 140 beats min^{-1} with normal variability.

Taking into account the patient's previous normal delivery and the small size of the fetus, it was decided to allow a trial of labour and to anticipate vaginal delivery. However, it was felt that there should be a low threshold for operative delivery. As the patient was not in established labour, the fetal heart rate decelerations, the need for maternal analgesia and the suspected rupture of membranes prompted a decision to induce labour by artificial membrane rupture with oxytocin augmentation. The patient appeared comfortable with the epidural solution being infused at a rate of 8 ml h^{-1}. Four hours after admission to the delivery suite, she delivered a healthy 2.2 kg boy by spontaneous vaginal delivery, who had an Apgar score of 10 at 5 min. She was transferred to a rehabilitation unit 2 days later.

Discussion

This is the first report, to our knowledge, of a pregnancy in which the fetus survived maternal PVS during the entire second and third trimesters, thus presenting a therapeutic dilemma during the pregnancy and at delivery of the fetus. PVS is a state of eyes-open unconsciousness with sleep–wake cycles in which patients are incapable of awareness of themselves or their environment.[2 3] The use of the term PVS usually implies that the vegetative state has continued for more than 1 month.[4] A patient in this state is not expected to recover, although this is the subject of controversy. There have been rare documented cases of late recovery of patients who had been diagnosed as being in a PVS.[5] Hence the diagnosis should be considered carefully before it is made because of the enormous financial, emotional and social implications of the management of these patients. Apart from establishing lack of awareness, the cause and irreversibility of the syndrome must be obvious.[6] The differential diagnosis includes prolonged coma (a state of unconsciousness in which the eyes are closed and sleep–wake cycles are absent) and the locked-in syndrome (resulting from brainstem lesions which disrupt the voluntary control of movement without abolishing either arousal or the content of awareness), both of which can also result from severe brain injury.[7]

Patients with PVS usually breathe spontaneously, although a tracheostomy may be necessary to ensure airway protection. Patients may exhibit a bizarre variety of neurological signs, including arousal to painful stimuli, grimacing, limb movement, spontaneous head movements, chewing, and grinding the teeth.[4] Most of these features were present in our patient, but with the additional feature that she was pregnant, exposing her to the potential risk of obstetric complications such as aortocaval compression, pregnancy-induced hypertension and premature labour. Termination of the pregnancy was not considered appropriate as the fetus had survived the hypoxic insult of a suicide attempt and had a good chance of survival as long as the mother was alive.

The choice of an appropriate place to manage the patient was a contentious issue. Managing her in a side room in the delivery suite would have been considered as a cheaper alternative to high-dependency or intensive care. However, this would not have provided optimal patient care in view of the presence of a tracheostomy tube and the lack of appropriate expertise in airway management among the labour ward staff. The potential requirement for artificial ventilation, the degree of nursing and physician input required and the obstetric and fetal risks indicated that the intensive care unit, rather than the high-dependency unit, was the most appropriate place to optimize her management. Once the fetus had been delivered without any maternal complications, the patient was deemed to present a risk profile similar to a non-pregnant patient in a PVS, who would usually be managed safely in a rehabilitation unit.

Assessment of pain and the provision of safe and effective analgesia during labour and delivery in a patient in a PVS is challenging because the patient cannot communicate. Physiological parameters such as tachycardia, hypertension and tachypnoea are commonly used as indicators of inadequate analgesia, but all lack specificity. The safety and efficacy of epidural analgesia for the management of labour pain is well documented.[8] Despite the absence of reports describing the use of epidural analgesia for a similar case, we could not find any justifiable reason for withholding epidural analgesia in our patient. We decided to use a plain bupivacaine infusion to avoid the further neurological depression that may have been induced by opioids. A continuous infusion, rather than bolus doses of epidural local anaesthetic, was chosen to minimize cardiovascular compromise, especially since dermatomal sensory levels of the block could not be assessed. The medical condition of the patient, the fetal heart rate decelerations in the intrapartum period and the anaesthetic considerations indicated a low threshold for emergency Caesarean section. Although regional anaesthesia is now established as the preferred technique for Caesarean section,[9] this requires a dense sensory block extending from the fourth thoracic dermatome to the fifth sacral dermatome.[10] However, we could not establish the extent of the block in this patient. Therefore, our anaesthetic plan in the event of emergency Caesarean section was to administer a general anaesthetic. Provision was made for a cuffed tracheostomy tube and antacid prophylaxis, as for any obstetric patient undergoing general anaesthesia. The epidural could also have been used for postoperative analgesia.

In conclusion, this unusual case illustrates that pregnant patients in a PVS may receive low-dose epidural analgesia in labour, but general anaesthesia would be indicated for Caesarean section. Nursing support, medical management, fetal assessment and deciding the optimum time for delivery are challenging decisions requiring a multidisciplinary approach to this clinical situation.

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BJA

EQUIPMENT

The Reflector: a new method for saving anaesthetic vapours

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Anaesthesia systems that minimize the use of volatile anaesthetics to reduce cost and pollution are of interest. Closed circuit anaesthesia is the ideal solution, but requires continuous adjustment of fresh gas flow and composition and thus is demanding in routine practice. We describe an alternative system, the Reflector system, which is open in regard to oxygen, nitrogen and N_2O, and semiclosed in regard to volatile anaesthetics. The Reflector system is a circle system with a carbon dioxide absorber and an automatic vapour delivery device placed in the inspiratory limb of the circle. A zeolite filter, the Reflector, is placed between the ventilator and the circle. The Reflector functions as a molecular sieve, preventing the volatile anaesthetic from leaving the circle. Isoflurane consumption using the Reflector system in bench tests and an animal study was compared with that of an open system. In bench tests consumption was reduced by 79% and 82%, at a respiratory frequency of 10 and 20 min^{-1}, respectively. The corresponding mean figures from the animal experiment were 65% and 77%.

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An anaesthesia circuit with carbon dioxide absorption was described in 1915 by Jackson.[1] In 1926, Waters[2] developed the to-and-fro absorption method, and the introduction of cyclopropane in 1933 led to widespread use of closed circuit anaesthesia.

With the clinical introduction of halothane in 1956 by Raventos,[3] low-flow and closed systems were used, but halothane vaporizers were imprecise at low gas flows, and lack of knowledge about the pharmacokinetics of halothane resulted in continued use of open/semiclosed systems.

The introduction of more ideal,[4] but also more expensive, inhalational anaesthetics and an increasing awareness of atmospheric pollution[5] have increased the interest in low-flow and closed circuit methods. These methods preserve humidity and body heat[6], save money[7] and reduce atmospheric pollution.

The greater use of gas monitors to measure inspired oxygen concentration[8] and other gases of the circuit has increased the safety of closed circuit anaesthesia. However, because they require continuous adjustments of gas delivery to the circuit,[9] these systems have not gained much popularity.

One solution could be a system that was open in regard to oxygen, nitrogen and N_2O delivery, but closed in regard to volatile anaesthetics. Such a system has been created by introducing a molecular sieve (Reflector),[10] a semipermeable filter that keeps the volatile anaesthetics on the patient side of the anaesthetic circuit but lets most other gases pass through. We evaluated such a Reflector system in bench tests and in an animal study.

Materials and methods

Set-up and experimental procedure

An anaesthesia circuit with one-way valves and a carbon dioxide absorber (Monosorb; Siemens Elema AB, Solna, Sweden) was used. The tubing was made of polyethylene (Hytrel). The Reflector was placed between a ventilator (Servo 900 C; Siemens Elema AB) and the circuit. A heat–moisture exchanger (Siemens Humidifier 152; Siemens Elema AB) was placed at the tracheal tube connector.

A computerized automatic vapour delivery device (AVDD)[11] was placed in the inspiratory limb of the circuit,

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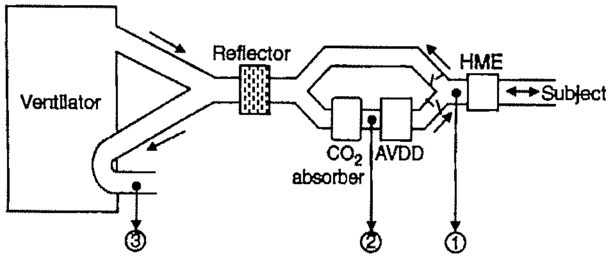

Fig 1 Set-up of the Reflector system AVDD, automatic vapour device HME, heat–moisture exchanger. The 'subject' is the connection to model lung or animal Numerals indicate gas sampling points

distal to the absorber. The AVDD delivered isoflurane at a partial pressure close to 40 kPa, the carrier gas being sucked from the circuit. During each inspiration, the AVDD continuously adjusted the addition of isoflurane vapour into the circuit to keep a set inspiratory isoflurane concentration of 1.5%. To allow continuous assessment of the isoflurane consumption, the reservoir of the AVDD was placed on an electronic balance (G1200; Ohaus, NJ, USA).

The ventilator delivered a gas mixture of 40% oxygen in nitrogen with a volume-controlled ventilatory pattern and constant inspiratory flow. The inspiratory time of the ventilatory cycle was 33% and the set end-expiratory pressure was set to 5 cm H_2O.

Side-stream gas analysers (Siemens 120; Siemens Elema AB), recirculating the sampled gas to the circuit, were used. Inspired, end-tidal and reflected isoflurane concentrations and inspired oxygen concentration were measured.

Measurements were also taken at the expiratory port of the ventilator to detect 'isoflurane breakthrough' (lower detection limit=0.1%), i.e. leakage of isoflurane on the ventilator side of the Reflector. The set-up of the Reflector system is shown in Figure 1.

The reflector

The Reflector consisted of a cylindrical plastic container, with a diameter of 70 mm, in which a 30 mm (RS30) or 50 mm (RS50) deep adsorption bed was arranged between two steel grids. A spreader was placed on each side to create laminar flow through the adsorption bed.

The pressure gradient over the RS30 was 1.2 and 4.6 cm H_2O at 0.5 and 1.0 litres s^{-1}, respectively, and that over the RS50 was 3.0 and 11 cm H_2O at 0.5 and 1.0 litres s^{-1}, respectively. The dead space of the plastic container, with the zeolite volume subtracted, was identical in both filters.

Pellets (110 or 185 ml) of ultrastable zeolite Y, a synthetic substance, were used as adsorption material. The pellets were about 1 mm in diamater and were prepared using about 15% by mass of a binder material (Al_2O_3).

Ultrastable zeolites are crystalline microporous silicates built up from corner-sharing $[SiO_4]^{4-}$-tetrahedral forming an indefinite framework structure, characterized by the presence of cavities and channels of well-defined shape and size (3–10 Å). Each type of zeolite has a unique framework structure, denoted by a three-letter code. Ultrastable zeolite Y is of the Faujasite (FAU) structural type, characterized by channels in three dimensions, with an aperture of 7.4 Å, connecting to microvoid cages (α(II) cages) within the structure. Ultrastable zeolites have high thermal stability (up to 1200°C) and are chemically inert; for example, they are insoluble in acids (except HF) and stable to alkali below pH 10.

Bench tests

Experiments were undertaken to compare isoflurane consumption by RS30 and RS50 with that by a non-rebreathing system. The different components of isoflurane consumption using the two Reflector systems were further studied. The reduction in isoflurane consumption by the added deadspace caused by the geometry of the Reflectors was evaluated using a dummy filter. This filter had a deadspace identical to that of RS30 and RS50 but was filled with glass spheres of 1 mm diameter. With connections all filters had a deadspace of 125 ml. To assess the amount of isoflurane lost due to 'isoflurane breakthrough', a Douglas bag, made of aluminium foil, was placed at the expiratory port of the ventilator. The amount of isoflurane trapped in the Reflector was also assessed by weighing the filter before and after each experiment

In bench tests the anaesthesia circle was connected to a lung model consisting of a U-shaped vessel filled with water. The end-expiratory volume of the model lung was 2.5 litres. The ventilator delivered 10 litres min^{-1} with a respiratory frequency of 10 and 20 min^{-1}. The inspiratory concentration of isoflurane was set to 1.5%.

In control experiments, the Y-piece of the ventilator tubing was connected directly to the model lung, creating an open system. The AVDD was placed in the inspiratory limb.

Animal experiments

After approval from the local Animal Studies Committee, two pigs (34 and 28 kg; one female and one male) were studied. The pigs were premedicated with 15 mg midazolam i.m. 30 min before anaesthesia. Anaesthesia was induced with ketamine i.v. 1.5 mg kg^{-1} and maintained with a continuous infusion of 7 mg kg^{-1} h^{-1}. Continuous infusion of pancuronium 0.35–0.50 mg kg^{-1} h^{-1} preserved muscle relaxation.

A tracheotomy was performed; control of the airway was achieved by a cuffed tube. A pressure transducer attached to a catheter placed in the carotid artery monitored arterial pressure. A central venous cannula was placed in the jugular vein and an i.v. infusion (glucose 25 g l^{-1} with 70 mmol Na^+, 45 mmol Cl^- and 25 mmol acetate per litre) was given at a rate of 6 ml kg^{-1} h^{-1}.

In the animal experiments only the RS30 was tested. The pigs were ventilated at a respiratory rate of 10 and 20 min^{-1} and tidal volume (V_t) was adjusted to keep end-tidal carbon

Table 1 The gravimetrically measured consumption at 1.5% inspired concentration of isoflurane RR=respiratory rate

System	Isoflurane consumption (g/90 min)	
	RR=10	RR=20
Open	100.7	102.6
Dummy	88.2	76.6
RS30	21.0	18.4
RS50	19.9	18.0

Table 2 Isoflurane consumption displayed in its different components using the Reflector system. RR=respiratory rate

System	Isoflurane consumption (g/90 min)			
	RS30		RS50	
	RR=10	RR=20	RR=10	RR=20
Dissolved in circuit and model lung	0.6	0.6	0.6	0.6
Uptake in filter	10.0	10.5	14.4	14.9
Loss through filter (breakthrough)	10.6	7.1	4.8	2.7

dioxide within 4.0–4.6 kPa. End-tidal carbon dioxide was measured with an in-line carbon dioxide analyser (Novametrix 7000, Wallingford, USA). A heat–moisture exchanger was placed at the tracheal tube. Inspiratory concentration of isoflurane was set to 1.5% throughout each experiment.

Each phase of the experiments, using the Reflector or the open system in a varied order, lasted 90 min. The zeolite material in the Reflector, when used, was renewed before a new experiment was started. Between each phase there was a 90 min washout period without a filter in the system. During the washout periods the end-expiratory isoflurane concentration decreased rapidly and no isoflurane was detectable after 30 min.

Calculation of measurement error

To verify the validity of isoflurane consumption in the open system, isoflurane expenditure was calculated (Tables 1 and 3) using 1.496×10^3 g litre^{-1} as isoflurane density at 25°C and 184.5 as molecular weight.[12]

The quantity of isoflurane used may differ from the calculated quantity because of measurement errors in the weight, the gas analyser and inaccuracy of the delivered volume from the ventilator. The measurement errors of the balance, gas analyser and ventilator are ±2%, ±5% and ±5% respectively, giving a combined measurement error of 7%.

Results

Bench tests

The calculated isoflurane consumption over 90 min using a ventilator flow of 10 litres min^{-1} and an inspiratory isoflurane concentration of 1.5% is 103.8 g. The gravimetrically measured isoflurane consumption values for the open system at a respiratory frequency of 10 s^{-1} and 20 s^{-1} (V_t 1000 and 500 ml) were 100.7 and 102.6 g, respectively.

Compared with the open system, the isoflurane consumption was reduced by 12% and 25% at a respiratory frequency of 10 and 20 min^{-1}, respectively, when using the Reflector system with the dummy filter. Compared with the open system, the RS30 reduced the consumption of isoflurane by 79% and 82%, respectively. The corresponding figures when using the RS50 were 80% and 82%. The absolute consumption is listed in Table 1.

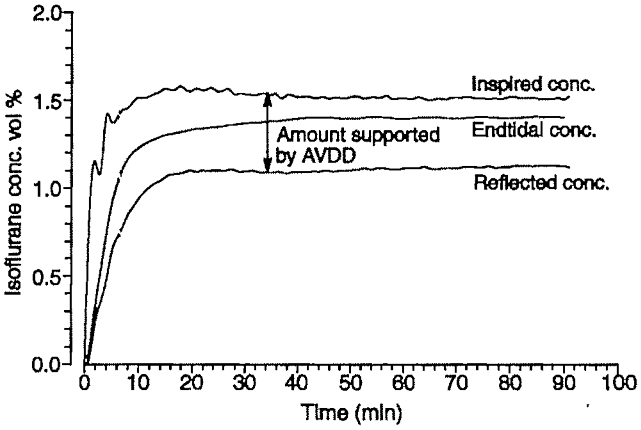

Fig 2 Tracing of mean inspired, end-tidal and reflected isoflurane concentrations in animal experiments using the Reflector system (RS30).

Using the RS30, 'breakthrough', or tracings ≥0.1% of isoflurane on the ventilator side of the Reflector, was detected after 30 min at a respiratory frequency of 10 s^{-1} (V_t 1000 ml) and after 44 min at a respiratory frequency of 20 s^{-1} (V_t 500 ml). No such breakthrough was detected with the RS50. The amount of isoflurane retrieved from the Douglas bag after 90 min sampling of scavenger gas and the gravimetrically measured weight gain of the filters are listed in Table 2.

Animal tests

In the reflector experiments (RS30), the inspired oxygen concentration was 37–40%. The preset inspired isoflurane concentration of 1.5 % was reached after 4 ± 2 min (mean ± SD) and kept at this level (±0.1%) by the AVDD. Within 10 min an end-tidal isoflurane concentration of at least 1.2% was reached. Reflection of isoflurane was detected within 1 min and rapidly reached a plateau of 1.1% within 15 min (Figure 2). Using the RS30, at a respiratory frequency of 10 or 20 min^{-1}, isoflurane consumption was reduced by 61–78% of that of an open system (Table 3).

In one pig, at a respiratory frequency of 10 min^{-1}, 'isoflurane breakthrough' was detected after 75 min.

Table 3 Calculated and gravimetrically measured isoflurane consumption in animal studies using the Reflector (RS30) and open systems after 30, 60 and 90 min V_t=tidal volume (mean±SD); RR=respiratory rate. * indicates breakthrough of isoflurane through the filter which happened after 75 min (pig 1 weighed 34 kg and pig 2 28 kg)

Pig #	System	RR (min^{-1})	V_t (litre)	Measured isoflurane consumption (g)			Calculated isoflurane consumption (g)		
				30 min	60 min	90 min	30 min	60 min	90 min
1	Reflector	10	1.00±0.05	12.3	19.0	24.3*			
2	Reflector	10	0.84±0.03	10.8	17.3	22.6			
1	open	10	0.78±0.03	26.3	52.1	76.8	27.0	54.0	80.9
2	open	10	0.60±0.04	21.4	38.4	57.9	20.8	41.5	62.3
1	Reflector	20	0.49±0.01	10.9	17.5	22.7			
2	Reflector	20	0.42±0.03	11.2	19.9	21.4			
1	open	20	0.48±0.01	35.9	70.8	104.8	33.2	66.4	99.6
2	open	20	0.39±0.02	29.0	56.4	84.2	27.0	54.0	80.9

Discussion

High gas flow administered to an anaesthesia circuit with carbon dioxide absorption is used as a standard technique by many anaesthetists. The inspired concentration of gases is close to the concentrations in the fresh gas delivered into the circuit. The major disadvantages of this approach are its expense and the loss of heat and humidity.

The Reflector system was designed as a simple high-flow system which is closed with regard to volatile anaesthetics, in this case isoflurane. This is achieved by inserting a zeolite filter at the interface between the anaesthetic circuit and the Y-piece from the ventilator (Figure 1). The ventilator provides the circle with fresh gas with each tidal volume. Because about 25% of carbon dioxide is reflected by the molecular sieve,[13] an anaesthesia circuit with a carbon dioxide absorber was used.

We compared the amount of isoflurane consumed using the open system with calculated values. The discrepancy between the calculated consumption of isoflurane and the amount used in the open system can be explained by measurement errors in the components, as consumption of an open system depends only on the delivered volume, if inspired volatile concentration is constant. Thus, the combined error of isoflurane consumption depends on the accuracy of the volume delivered by the ventilator, the inspired isoflurane concentration measured by the gas analyser and the accuracy of the balance. This error was calculated as 7%, and all the measured values were within this level.

Assessment of the Reflector system in bench tests was done by comparing a zeolite filter with a dummy filter, using an open system as control. The reduction of isoflurane consumption when changing from the open system to the Reflector system, but using a dummy filter filled with glass spheres, was caused by the added deadspace of this filter when situated between the ventilator and the circle and was more pronounced at high ventilatory frequencies equal to low tidal volumes.

Zeolite can reflect the expired isoflurane and thereby retain the volatile anaesthetic in the circle system. The microporous arrangement of the zeolite gives rise to a large internal surface area (1000 m^2 g^{-1}) and microvoid space (0.5 cm^3 g^{-1}). Because of the connectivity of the tetrahedral building units, all oxygen atoms in the three-dimensional framework are interconnected and shared between two silicon atoms: there are no terminal hydroxyl groups. This makes the (internal and external) surfaces of the zeolite hydrophobic. Together with the size of the micropores, this gives ultrastable zeolite Y a high affinity and a high adsorption capacity for non-polar substances, e.g. volatile anaesthetics, and a low affinity for polar substances, e.g. water. The size and shape of the molecules entering the pore system, i.e. the aperture of the channels, restrict the adsorption. The amount adsorbed depends on several factors, including the partial pressure, molecular weight, polarity and polarizability of the adsorbate and on the temperature.

We found that both RS30 and RS50 reduced isoflurane consumption by about 80% compared with the open system. Our results support the findings of Thomasson, Luttrop and Werner[10] using a similar filter but a different set-up. However, in a truly closed system the amount of isoflurane used should only be equivalent to the volume of the circle and test lung, saturated to 1.5%, in this set-up approximately 0.6 g of isoflurane.

Isoflurane use during Reflector experiments was greater than that in a closed system because of 'isoflurane breakthrough', the passage of volatile anaesthetics through the Reflector and absorption of vapour in the molecular seive of the Reflector. Breakthrough was more pronounced at a large tidal volume while absorption was independent of respiratory frequency.

Increasing the amount of zeolite in the filter, from the RS30 to the RS50, did not increase efficacy because each millilitre of zeolite added to the absorption bed traps about 0.1 g of isoflurane when saturated. Therefore, increasing the amount of zeolite to prevent loss through the filter, was in this case, offset by the amount of isoflurane trapped in the filter. Lengthy anaesthesia will be more cost effective, as will the reuse of a loaded filter.

The difference between isoflurane use in the open pig experiments (Table 3) and that in the open bench tests

(Table 1) was caused by differences in tidal volume, which were necessary to keep end-tidal carbon dioxide within normal limits.

In the animal experiment, isoflurane consumption by the open system and the RS30 was not quite comparable because the tidal volumes used were higher in the RS30. One reason was that the volume of this system was 2 litres greater, which increased the compressible volume. Futhermore, end-tidal carbon dioxide was only kept within the limit of 4.0–4.6 kPa.

The calculated uptake of isoflurane by the pigs in our experiments was 8–9 g.[14] The reduction in concentration of isoflurane in the expired air, caused by uptake of isoflurane by the pig, may ease the burden on the zeolite filter (RS30) as suggested by the fact that 'isoflurane breakthrough' was always found in the bench tests but only detected in one phase of the animal experiments. Uptake by the pigs was similar to the amount of isoflurane lost through the filter (RS30) in bench tests, thus explaining the small difference between consumption in the bench tests and animal experiments.

In conclusion, by using a ventilator attached to the circle system with a zeolite reflector placed in between, isoflurane consumption is reduced by approximately 80% in a bench test and approximately 70% in an animal study.

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COMMENTARY

Management of massive blood loss: a template guideline

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The management of acute massive blood loss is considered and a template guideline is formulated, supported by a review of the key literature and current evidence. It is emphasized that, if avoidable deaths are to be prevented, surgeons, anaesthetists, haematologists and blood-bank staff need to communicate closely in order to achieve the goals of secure haemostasis, restoration of circulating volume, and effective management of blood component replacement.

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Complications of major blood loss and massive transfusion may jeopardize the survival of patients from many specialties, and challenge haematological and blood transfusion resources.

Avoidable deaths of patients with major haemorrhage are well recognized,[1] [2] and locally agreed and/or speciality-specific guidelines[3] are needed to ensure effective management. Current UK published guidelines[4] [5] [6] are based on historical transfusion practice and are not easily referred to in an emergency situation. A symposium on massive transfusion was organized by the National Blood Service Northern Zone in December 1998 and was attended by anaesthetists, traumatologists, haematologists, nurses and blood-bank personnel. At the conclusion of the meeting, a number of key principles were agreed and, in consultation with delegates, a guideline document was produced and is now available in hospitals served by the Leeds, Liverpool, Manchester, Newcastle and Trent Blood Centres as a basis for local protocols.

The guideline is presented in this article (Table 1) as a simple template which may be modified to take into account local circumstances and displayed in clinical areas. The left-hand column of the template outlines the key steps or goals, the centre column adds procedural detail and the right-hand column provides additional advice and information.

The accompanying commentary is not intended to be an exhaustive review, but provides key references on which the recommendations are based.

The Hospital Transfusion Committee has a central role in ensuring the optimum and safe use of blood components. The development of protocols for the management of massive transfusion is an important part of the remit of such committees and it is hoped that this article will facilitate this process.

Commentary

Background

Massive blood loss is usually defined as the loss of one blood volume within a 24 h period,[7] normal blood volume being approximately 7% of ideal body weight in adults and 8–9% in children. Alternative definitions include 50% blood volume loss within 3 h or a rate of loss of 150 ml min^{-1}.[8] Such definitions emphasize the importance of the early recognition of major blood loss and the need for effective action to prevent shock and its consequences.

Priorities for treatment are:

- restoration of blood volume to maintain tissue perfusion and oxygenation;
- achieving haemostasis by:
  - treating any surgical source of bleeding;
  - correcting coagulopathy by the judicious use of blood component therapy.

A successful outcome requires prompt action and good communication between clinical specialties, diagnostic laboratories, blood-bank staff and the local blood centre. Blood component support takes time to organize and the blood centre may be up to 2 h away from the hospital.

Early consultation with surgical, anaesthetic and haematology colleagues is advisable, and the importance of good communication and cooperation in this situation cannot be

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Table 1 Acute massive blood loss. template guideline

Goal	Procedure	Comments
Restore circulating volume	Insert wide-bore peripheral cannulae Give adequate volumes of warmed crystalloid, ?colloid, blood Aim to maintain normal blood pressure and urine output >30 ml h^{-1}	14 G or larger Monitor central venous pressure Blood loss is often underestimated Refer to Advanced Trauma Life Support guidelines Keep patient warm
Contact key personnel	Clinician in charge Duty anaesthetist Blood bank Duty haematologist	Nominated coordinator should take responsibility for communication and documentation
Arrest bleeding	Early surgical or obstetric intervention Interventional radiology	
Request laboratory investigations	FBC, PT, APTT, fibrinogen; blood-bank sample, biochemical profile, blood gases or pulse oximetry Ensure correct sample identity Repeat FBC, PT, APTT, fibrinogen every 4 h or after 1/3 blood volume replacement Repeat after blood component infusion	Take samples at earliest opportunity as results may be affected by colloid infusion Misidentification is commonest transfusion risk May need to give components before results available
Request suitable red cells	Un-crossmatched group O Rh negative In extreme emergency No more than 2 units	Rh positive is acceptable if patient is male or postmenopausal female
	Un-crossmatched ABO group-specific When blood group known	Laboratory will complete cross-match after issue
	Fully cross-matched If irregular antibodies present When time permits	Further cross-match not required after replacement of 1 blood volume (8–10 units)
	Use blood warmer and/or rapid infusion device.	Blood-warmer indicated if flow rate >50 ml kg^{-1} h^{-1} in adult
	Employ blood salvage if available and appropriate	Salvage contraindicated if wound heavily contaminated
Request platelets	Allow for delivery time from blood centre Anticipate platelet count <50×10^{9} litre^{-1} after 2 × blood volume replacement	Target platelet count: >100×10^{9} litre^{-1} for multiple/CNS trauma or if platelet function abnormal >50×10^{9} litre^{-1} for other situations
Request FFP (12–15 ml kg^{-1} body weight= 1 litre or 4 units for an adult)	Aim for PT and APTT <1.5× control mean Allow for 30 min thawing time	PT and APTT >1.5× control mean correlates with increased surgical bleeding
Request cryoprecipitate (1–1.5 packs/10 kg body weight)	Replace fibrinogen and factor VIII	Fibrinogen <0.5 strongly associated with microvascular bleeding
	Aim for fibrinogen >1.0 g litre^{-1} Allow for delivery time plus 30 min thawing time	Fibrinogen deficiency develops early when plasma-poor red blood cells used for replacement
Suspect DIC	Treat underlying cause if possible	Shock, hypothermia, acidosis leading to risk of DIC Mortality from DIC is high

overemphasized. A member of the clinical team should be nominated to act as the coordinator responsible for overall organization, liaison, communication and documentation. This is a critical role for a designated member of the permanent clinical staff. The Hospital Transfusion Committee should provide a forum in which a rapid communication cascade can be agreed and massive transfusion episodes reviewed.

Resuscitation

Prolonged oligaemic shock carries a high mortality rate because of organ failure and disseminated intravascular coagulation. Restoration of circulating volume is initially achieved by rapid infusion of crystalloid or colloid through large-bore (14 gauge or larger) peripheral cannulae.[9] The use of albumin and non-albumin colloids versus crystalloids for volume replacement has recently been the subject of debate after two controversial meta-analyses,[10 11] and the use of colloid is not recommended in the latest American College of Surgeons Advanced Trauma Life Support Guidelines.[12] Further trials are required before firm recommendations can be made.

Red cell transfusion is likely to be required when 30–40% of blood volume is lost; the loss of over 40% of blood volume is immediately life-threatening.[12] Hypothermia increases the risk of disseminated intravascular coagulation and other complications[12] [13] and may be prevented by prewarming the resuscitation fluids, patient-warming devices such as warm air blankets, and the use of temperature-controlled blood warmers.

Blood loss is usually underestimated, and it must be remembered that haemoglobin and haematocrit values do not fall for several hours after acute haemorrhage.[9]

For acutely anaemic patients, the American Society of Anesthesiologists Task Force on Blood Component Therapy has concluded, on the basis of the available evidence, that transfusion is rarely indicated when the haemoglobin concentration is >10 g dl^{-1} but is almost always indicated when it is <6 g dl^{-1}.[14] Determination of whether intermediate haemoglobin concentrations justify red cell transfusion should be based on the patient's risk factors for complications of inadequate oxygenation, such as the rate of blood loss, cardiorespiratory reserve, oxygen consumption and atherosclerotic disease. Measured cardiological variables, such as heart rate, arterial pressure, pulmonary capillary wedge pressure and cardiac output, may assist the decision-making process, but it should be emphasized that silent ischaemia may occur in the presence of stable vital signs.

Intraoperative blood salvage may be of great value in reducing the requirement for allogeneic blood, but bacterial contamination of the wound is a relative contraindication.[15]

Investigations

Blood samples should be sent to the laboratory at the earliest possible opportunity for blood grouping, antibody screening and compatibility testing, as well as for baseline haematology, coagulation screening, including fibrinogen estimation and biochemistry investigations.

When dealing with an evolving process, it is important to check the parameters frequently (at least four-hourly and after each therapeutic intervention) to monitor the need for and the efficacy of component therapy.

Expert advice should be sought from a haematologist regarding appropriate investigations, their interpretation and the optimum corrective therapy.

Blood component therapy

Red cells

In an extreme situation it may be necessary to use group O un-crossmatched red cells if the blood group is unknown. In an emergency, premenopausal females whose blood group is unknown should be given ORh(D) negative red cells in order to avoid sensitization and the risk of haemolytic disease of the newborn in subsequent pregnancy. It is acceptable to give ORh(D) positive cells to males and postmenopausal females of unknown blood group.[16] Group-specific red cells should be given at the earliest possible opportunity as group O blood is a scarce resource.

It is important to bear in mind that most transfusion-related morbidity is due to incorrect blood being transfused.[17] It is therefore essential that protocols are in place for the administration of blood and blood components[18] and that these are adhered to even in an emergency situation.

All blood components supplied by the UK transfusion services are now leucodepleted and the blood bank will provide red cells in optimal additive solution, containing virtually no plasma, platelets or leucocytes. The benefits of leucodepletion include reduced non-haemolytic febrile transfusion reactions, reduced transmission of leucocyte-associated viruses, such as cytomegalovirus, and reduced immunosuppressive effects of transfusion.[19] An additional microaggregate filter is not necessary.

Platelets

Expert consensus argues that platelets should not be allowed to fall below the critical level of 50×10^9 litre^{-1} in acutely bleeding patients.[20] A higher target level of 100×10^9 litre^{-1} has been recommended for those with multiple high-energy trauma or central nervous system injury.[21] [22] Empirical platelet transfusion may be required when platelet function is abnormal, as is found after cardiopulmonary bypass.

A platelet count of 50×10^9 litre^{-1} is to be anticipated when approximately two blood volumes have been replaced by plasma-poor red cells,[23] but there is marked individual variation. In assessing the requirement for platelets, frequent measurements are needed, and it may be necessary to request platelets from the blood centre at levels above the desired target in order to ensure their availability when needed.

Fresh frozen plasma (FFP) and cryoprecipitate

Most clinical studies and guidelines have been based on the use of whole blood or plasma-reduced red cells, which contain some residual coagulation factor activity. Nowadays, red cell replacement is likely to be in the form of plasma-poor red cells suspended in optimal additive solution, in which coagulation factor activity is negligible. Under these circumstances, coagulation factor deficiency is the primary cause of coagulopathy. The level of fibrinogen falls first; the critical level of 1.0 g litre^{-1} is likely to be reached after 150% blood loss, followed by decreases in other labile coagulation factors to 25% activity after 200% blood loss.[23] Prolongation of activated partial thromboplastin time (APTT) and prothrombin time (PT) to 1.5 times the mean normal value is correlated with an increased risk of clinical coagulopathy[24] and requires correction.

Laboratory tests of coagulation should be monitored frequently and interpreted with advice from a clinical haematologist; laboratories should have in place standard operating procedures to ensure that clinical staff are contacted appropriately. Experienced laboratory staff should be empowered to issue blood components in the first instance using a locally agreed algorithm. It may be necessary to request components before results are available, depending on the rate of bleeding and the laboratory turnaround time. Although 'formula replacement' with fresh plasma is not recommended, it has been suggested that infusion of FFP should be considered after one blood volume has been lost.[25] The dose should be large enough to maintain coagulation factors well above the critical level, bearing in mind that the efficacy may be reduced because of rapid consumption.[21 25]

FFP alone, if given in sufficient quantity, will correct fibrinogen and most coagulation factor deficiencies, but large volumes may be required. If fibrinogen levels remain critically low (<1.0 g litre^{-1}), cryoprecipitate therapy should be considered.[21 25]

The Guidelines on Oral Anticoagulation of the British Committee for Standards in Haematology recommend prothrombin complex concentrate as an alternative to FFP when major bleeding complicates anticoagulant overdose.[26] It should be remembered, however, that these preparations are potentially thrombogenic and the role of specific coagulation factor concentrate outwith hereditary bleeding disorders is unproven.

Disseminated intravascular coagulation (DIC)

DIC is a feared complication in the acutely bleeding patient. It carries a considerable mortality rate, and once established it is difficult to reverse. At particular risk are: patients with prolonged hypoxia or hypovolaemia; patients with cerebral or extensive muscle damage; and patients who become hypothermic after infusion of cold resuscitation fluids. Laboratory evidence of DIC should be sought before microvascular bleeding becomes evident so that appropriate and aggressive action can be taken to address the underlying cause. Frequent estimation of platelet count, fibrinogen, PT and APTT is strongly recommended; measurement of fibrinogen degradation products or D-dimers may be useful. Prolongation of PT and APTT beyond that expected by dilution, together with significant thrombocytopenia and fibrinogen of <1.0 g litre^{-1}, are highly suggestive of DIC.

Treatment consists of platelets, FFP and cryoprecipitate, given sooner rather than later, in sufficient dosage but avoiding circulatory overload.

Discussion

A guideline has been defined as 'a systematically developed statement that assists in decision-making about appropriate health care for specific clinical situations'.[27] Successful implementation will depend on local ownership by adaptation to local circumstances and accessibility at the point of clinical activity.

In developing this template guideline, we have examined such sound scientific evidence as is available, reviewed the relevant literature and professional consensus statements, and taken into account discussion and comment from contributors and delegates at the National Blood Service Northern Zone Symposium on Massive Transfusion.

The recommendations contained in these guidelines must be regarded as Grade C, based as they are on uncontrolled observational studies and a consensus of expert opinion (Level 3 evidence). Well-designed case–control studies and randomized clinical trials are lacking in this important area of transfusion medicine.

A recent cohort study[28] shows a significantly improved survival rate in massively transfused patients over a 10-yr period and associates this with more effective and efficient rewarming techniques, aggressive resuscitation and component therapy, and improved blood-banking.

There is a need for further studies to clarify these issues and provide firm evidence on which future recommendations can be based.

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General *versus* regional anaesthesia for hip fracture surgery

Editor—The article by Urwin and colleagues[1] appears to be based on the unstated assumption that all general anaesthetics are alike and all regional anaesthetics are alike. That is, 'regional' and 'general' define two homogeneous categories whose effects may be compared. Given the diverse actions of different general and different regional anaesthetics, is this a reasonable assumption?

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1 Urwin SC, Parker MJ, Griffiths R. General versus regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials. *Br J Anaesth* 2000; **84**: 450–5

Editor—Thank you for the opportunity to reply to the letter by Eger about our article. Most of the patients involved in the meta-analysis received a spinal anaesthetic, with less than 5% receiving an epidural anaesthetic. Although different local anaesthetics were used, all are known to have similar actions at the sodium channel, and therefore can be expected to have equivalent peripheral effects. It may have been prudent to exclude the paper employing epidural anaesthesia, but this was included for completeness. General anaesthetics were included in a single group, as there is still no consensus of opinion as to their mode of action. There is no evidence by which data relating to each type of general anaesthetic could be separated according to mode of action. We recommend further randomized controlled trials to compare regional and general anaesthesia for hip fracture, which would include a standardized technique for both regional and general anaesthesia.

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Off-pump revascularization and the brain

Editor—We read with interest the editorial by Alston on cerebral outcome after beating heart coronary artery surgery.[1] We agree that the potential benefits of off-pump coronary artery surgery are currently incompletely investigated, and that the evidence to date is based on retrospective and non-randomized studies. However, off-pump surgery in its current form is a new procedure, and many surgeons have only recently completed the learning curve for it. A recent paper by De Leval and colleagues[2] indicates that the development of new operations in surgery may be associated with a higher morbidity and mortality in the initial phase as the technique is refined but may lead to important benefits in the long term. It would not be appropriate to undertake randomized controlled trials of beating heart coronary surgery versus conventional techniques before the learning curve was reaching its plateau.

In our institution, we have had a beating heart programme for over 2 years and have watched our results improve to a level comparable to conventional CABG in selected cases. Following a review of our progress in this field, we felt justified in undertaking a prospective, randomized trial investigating exactly those outcomes highlighted in your editorial, i.e. neuropsychological outcome, cerebral damage and quality of the distal coronary anastomoses as assessed by angiography at 3 months. We have developed a rigorous study protocol with the participation of surgeons, anaesthetists, cardiologists and the clinical trials unit at the Royal Brompton Hospital. The first patients were recruited in February 2000.

The Bristol group have already published results of randomized trials they have completed in this field.[3 4] It would appear that other units also have randomized trials at the planning stage.

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Editor—We applaud Alston's editorial and analysis[1] of the Short Communication by Watters and colleagues[2] reporting reduced cerebral microembolic signals during off-pump coronary artery bypass (OPCAB) surgery. While the latter publication indeed provides more circumstantial evidence that avoiding cardiopulmonary bypass (CPB) is better for the brain, published data on clinical (cognitive) outcome remains, at best, equivocal. Watters and colleagues correctly advised caution in extrapolating their findings to neurological outcome.

As we move into the era of *Clinical Governance*, *Clinical Excellence* and evidence-based practice, it is essential that novel surgical procedures, such as OPCAB, are evaluated in a fashion similar to new drugs. Perhaps OPCAB should be subjected to the same scrutiny as have transmyocardial laser revascularization and lung volume reduction surgery. Only a well-powered, multicentre,

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randomized controlled trial will permit any claim of superior neurological outcome to be substantiated. For this reason it has been argued that to conduct elective OPCAB outside the boundaries of such a study would be morally questionable.[3]

For many cardiac surgical patients, however, CPB remains a necessary and unavoidable evil. Progress in off-pump coronary revascularization should not be allowed to impede improvements in extracorporeal circulation technology.

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Editor—I thank Arrowsmith and Large for their interest in my editorial on the implications of off-pump coronary artery bypass grafting (CABG) surgery on the brain. They have my agreement that off-pump CABG surgery should be objectively evaluated. With even greater certainty, I agree that such surgery should not be clinically advocated on the basis of superior cognitive or neurological outcome unless such claims become substantiated. However, I am not party to the view of Ali and Large that off-pump CABG surgery should not be conducted outside the bounds of such a study[1] as, presently, this would be excessively proscriptive. Currently, to dictate such a narrow application of what is a clearly practical and widely used surgical technique, as well as one that has the potential to reduce the morbidity associated with CABG surgery, would stifle its development. Evaluating a new surgical technique is far less straightforward than a new drug or piece of equipment. First, surgeons and anaesthetists have to refine and adjust their techniques before optimum results are obtained and this takes time and experience. Until this is achieved in a sufficient number of centres, there is little point in attempting to compare the morbidity and mortality of performing CABG surgery on- or off-pump. However, as I stated in my editorial, that time must be fast approaching. Until such studies are conducted, and as long as patients are made fully aware that they are not receiving conventional treatment, off-pump CABG surgery should be a treatment option for those who have suitable patterns of coronary artery disease.

For these reasons, I thank Haxby and colleagues for their comments as they align with my own views. They also have my gratitude for bringing to my attention two randomized controlled trials comparing CABG surgery on- and off-pump that had not been published when the editorial was submitted. Of the two studies, Lloyd and colleagues' paper is pertinent to my editorial as it examined S-100β levels and cognitive change in patients undergoing CABG surgery on- and off-pump.[2] Notably, they found on-pump patients had but slightly higher levels of S-100β at one time point compared to those undergoing off-pump surgery and, more importantly, there was no difference in cognitive outcome between the groups. This study would suggest that undertaking CABG surgery off-pump has no important benefits, in terms of cerebral damage, over that done with CPB. As much as the study should lend caution to making unsubstantiated claims as to the value of one form of CABG surgery over another, it is at least reassuring to find that cognitive outcome is no worse off- than on-pump. What has now to be established, using a randomized controlled study, is whether high quality coronary anastomoses can be as well achieved off- as on-pump. For this reason, I applaud Haxby and colleagues for their approach and look forward to hearing the results of their research.

Every year, cardiopulmonary bypass enables the surgical treatment of hundreds of thousands of patients who suffer congenital heart, heart valve and coronary artery disease. Even if it proves to be the superior technique, off-pump CABG surgery will not be a viable option for many patients who have unsuitable patterns of coronary artery disease. For these patients, and those with congenital or heart valve disease, cardiopulmonary bypass will remain the keystone to their surgical treatment for all of the foreseeable future. I, therefore, fully endorse the opinion expressed by Arrowsmith and Large that the development of off-pump CABG surgery should in no way impede improvements in cardiopulmonary bypass.

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1 Ali ZA, Large SR. Key Outcomes '99: Gone West? *Ann Thorac Surg* 2000; **69**: 336
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Intubating laryngeal mask airway (ILMA) seems to be an ideal device for blind intubation in case of immobile spine

Editor—The study of Wakeling[1] in which he described the use of the ILMA to intubate blinding the trachea in 10 normal subjects who were wearing a stiff neck collar, and applying cricoid pressure in a simulated trauma scenario exhibited a low success rate. The conclusions in this small study were far-reaching in that they recommend not to use an ILMA in patients with immobile spine.

Ferson and associates[2] published an extensive series of 126 patients including 28 patients with a difficult airway of whom eight had an unstable spine. All were successfully ventilated and intubated through the ILMA. In addition, Rosenblatt and Murphy[3] published two cases of patients wearing a rigid cervical collar with laryngeal oedema and emphysema who could easily be ventilated and intubated on the first attempt using an ILMA after a sequence of failed direct laryngoscopies. One of these patients showed a small fracture of the anterior surface of C6, but had no neurological deficit.

We examined retrospectively 17 cases of blind intubation through the ILMA in patients with disorders of the cervical spine who were wearing a stiff neck collar. Patients presented either an unstable dens fracture ($n = 5$); other fractures of the cervical spine ($n = 5$); cervical disc herniation with incomplete paraparesis ($n = 4$); subluxation of the cervical spine ($n = 1$); traumatic destruction of intervertebral discs and paresis of the right arm ($n = 1$); or vertebral abscess extending to the parapharyngeal space ($n = 1$). There were six female and 11 male patients with a median age of 64.3 years (range 38–86 years), a mean weight of 69.2 kg and a mean height of 170.1 cm. After induction of anaesthesia with fentanyl, thiopentonal, propofol or etomidate, and neuromuscular blockade with atracurium or cisatracurium, ventilation and an adequate depth of anaesthesia were maintained by face mask ventilation with isoflurane and nitrous oxide in oxygen. We did not carry out direct laryngoscopy and did not apply cricoid pressure to prevent compression of the spinal cord. In 16 patients (94.1%) insertion of the ILMA caused no difficulty, while in one patient insertion was rendered more difficult because of impaired mouth opening due to the stiff neck collar, but could be managed by rotating the ILMA into a paramedian position. Optimum conditions for ventilation through the ILMA could be achieved at the first attempt in 10 patients (58.8%) while 2–4 attempts were necessary in seven patients (42.2%, mean number of insertion attempts, 1.56). Shortlived laryngospasm occurred in two patients (11.8%) after ILMA insertion due to inadequate depth of anaesthesia. Successful intubation could be performed in all 17 patients, in nine at the first attempt (52.9%). In seven patients (47.1%) 2–3 attempts to intubate were necessary while in one patient 10 attempts were performed (mean number of intubation attempts, 2.1). At the end of surgery and anaesthesia none of these patients showed signs of neurological deterioration.

In addition, it is important to consider the cricoid pressure applied in the trauma scenario, as its success is by no means clarified. In the light of the five patients who were easy to intubate when they had the collar removed in Wakeling's study we must assume that no cricoid pressure was applied. Analysing the literature there are numerous hints that cricoid pressure impedes positioning and ventilation with the standard laryngeal mask airway (SLMA),[4 5 6] as well as placement and intubation through an ILMA.[7]

After insertion, the ILMA was gently adjusted to find the position of optimal seal and this procedure was repeated before another intubation attempt. According to our experience we propose inserting the ILMA deeper instead of focusing on the best seal position. In the position of best ventilation, the epiglottic elevating bar might not be able to lift up the epiglottis totally. This corresponds to our fibreoptic findings. In one of our studies comparing intubation success through the SLMA and the ILMA the fibreoptic view in 14 patients showed the epiglottis in the lumen of the shaft in nine patients in the ILMA group and in 11 in the SLMA group. We found a degree of obstruction by the epiglottis in 43% of patients with the ILMA and 52% with the SLMA.[8] In the light of these findings, the position of best seal might not be the best predictor of intubation success. Moreover, according to the inventor, we suggest with an 'up-down' manoeuvre to place the device correctly in position, intubation is highly effective.[9]

The authors do not mention the internal diameter (ID) of the Euromedical tracheal tubes used. We suspect it could be too large. We suggest, particularly in emergency cases, use of the small tubes, such as 6 mm ID. Moreover one of the patients (subject no. 8) with a body height of 152 cm could not be intubated blindly via an ILMA size 5; this failure might be due to the use of an inappropriate ILMA size.

Our results show that in the vast majority of patients the stiff neck collar produced no serious obstacle to insertion, ventilation and blind intubation through the ILMA. Problems in ventilation and intubation were mostly caused by an inappropriate sized (mostly too small) ILMA, and inadequate depth of anaesthesia. We suggest that conclusions reported in a model scenario and a very small group cannot be used in clinical practice and above all not in relation to the device itself, particularly concerning cricoid pressure which interferes with successful ventilation as well as intubation.

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Editor—We were delighted to read the correspondence from Drs Möller, Andres and Langenstein and appreciate the chance to reply. They say that our study had a small number of patients. We had intended to enrol 50 subjects but decided to abandon the study after 10 because of the high failure rate. We were particularly interested to determine whether the ILMA would reliably enable intubation in patients wearing a semi-rigid neck collar with cricoid pressure applied in a simulated emergency situation. Airway control in the emergency environment is of vital importance and for a new technique to be recommended it must be reliable, safe and have a higher degree of success than the currently accepted approach. Our results clearly showed a much lower degree of success with the ILMA than direct laryngoscopy during in-line stabilization.

Ferson and colleagues[1 2] successfully intubated eight patients with an unstable cervical spine using the ILMA but make no reference to how the spine was managed during intubation. Rosenblatt and Murphy[3] recorded three case reports of ILMA intubation with cervical collars in place. There is unfortunately no mention of the collar type, size or adequate fitting. Indeed one patient had 3.5 cm mouth opening despite the collar which implies loose fitting. In addition, this group used precurved PVC tubes which project at a different angle from the ILMA and are much stiffer than the recommended Euromedical tracheal tubes. This may have contributed to intubation success but these tubes are associated with a high incidence of sore throat and hoarseness implying mucosal damage.[4] After failed intubation with direct laryngoscopy the ILMA clearly has a role but not as the primary airway management technique.

Möller and colleagues' data on 17 patients is interesting. We had difficulty inserting the ILMA in virtually all patients although they report difficulty in only one. Possibly this was due to the use of a different type of collar or one more loosely applied? Otherwise, their data fully supports our conclusions that the ILMA is unsuitable for use with a neck collar in the emergency situation. They reported that only 59% of patients could be satisfactorily ventilated and only 54% intubated at the first attempt. One patient required 10 intubation attempts. This would not be acceptable in the emergency setting.

There is little doubt that cricoid pressure affects standard LMA and ILMA positioning during insertion; however, it is less clear whether cricoid pressure applied after ILMA insertion affects intubation success. It was for this reason that we removed cricoid pressure momentarily during ILMA insertion but it remained otherwise applied during all intubation attempts including those made after collar release. Our 100% first time success rate after collar release despite cricoid pressure implies that this manoeuvre has little effect on intubation.

We were interested to read of their experience with inserting the ILMA deeper to improve the success rate rather than finding the best seal. It is unfortunate that these data are unpublished. In our experience the best seal is usually obtained by a gentle rotation of the ILMA in the sagittal plane which tends to insert the ILMA slightly deeper whilst lifting the larynx slightly. We may therefore be describing the same phenomenon.

We do not believe that the 7.0 and 7.5 mm internal diameter tracheal tubes were too large which is evidenced by the lack of intubation difficulty experienced once the collar had been released. The use of a size 5 ILMA for subject 8 was accurate because the thyromental distance was >7 cm despite the patient being only 152 cm tall. He was intubated first time once the collar had been released, to prove this point.

We disagree totally with the conclusions made on their own data. Whatever the reasons for the failure to ventilate and intubate, their first time success rates were only 59% and 53%. This could not be acceptable in the emergency setting as it would be far less reliable than the current ATLS recommended approach to emergency airway management.[5]

We believe that the ILMA may be used in patients with an immobilized cervical spine in the elective situation where there is time to proceed safely. However, despite a 'very miniature collection' we strongly believe that our findings can be extended to the real setting and that this is supported by the data from Möller and colleagues.

Use of the ILMA is clearly far less reliable in a rigid cervical collar than manual in-line stabilization and direct laryngoscopy. It cannot therefore be recommended to supercede currently accepted emergency airway management where neck injury is yet to be excluded.

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1 Ferson DZ, Brimacombe J, Brain AIJ, Verghese C. The intubating laryngeal mask airway. *Int Anesthesiol Clin* 1998; **36**: 183–209
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Preparation for regional anaesthesia induces changes in thromboelastography

Editor—We read with interest the Short Communication by Gorton and colleagues relating thromboelastographic (TEG) changes to environmental factors in preparation for regional anaesthesia.[1] The study poses some questions for further research, but we would like to comment on a few issues covered in the paper

We disagree that haemodilution with a single fluid (Gelatin) *in vivo* can be extrapolated into questioning the whole issue of hypercoagulability associated with moderate haemodilution. What these authors have effectively demonstrated is that, in patients awaiting Caesarean section, a moderate increase in coagulation status can be demonstrated shortly after placement of intravenous cannulae. The volume of fluid administered was less than 10 per cent of the circulating blood volume in these pregnant patients, and therefore probably too small to exert any demonstrable effect on coagulation.

The 'stress-response' is well known to cause a hypercoagulable state, for the reasons cited by Gorton. It is understandable that there could have been a brief period of hypercoagulability after a period of monitoring following cannulation directly outside theatre prior to Caesarean section We have demonstrated a similar effect in blood donors where we showed an increase in coagulability of blood at 15 min after venesection, but this effect had disappeared by 1 h (study in progress). Also of relevance to interpretation of these results is the length of time the 22 gauge cannula was *in situ* prior to the second sampling, and if any fluids had been infused into this cannula, as this may affect coagulation. It is unclear if the second sampling was from a fresh venepuncture or from a second indwelling 22G cannula sited at the start. At the time of our *in vivo* study, we tested the effect of cannula placement on coagulation, and showed that the placement of a cannula alone increased coagulation, but that this effect was absent provided fluids were infused through this cannula, implying that fluid infusion 'washed away' activated coagulation factors from the puncture site.

The specific fluid used undoubtedly has an effect on TEG variables. Crystalloid haemodilution leads to a greater hypercoagulability than colloid intravenous fluids[2–4] The paper by Egli and Zollinger[5] is incorrectly cited by Gorton and colleagues as showing a decrease in coagulability with *in vitro* haemodilution. Egli and Zollinger showed an *increase* in coagulability with 30% crystalloid haemodilution that returned to baseline at 60%, apart from a decrease in MA. What Egli referred to was a decrease in coagulability only with gelatin and albumin at severe (60%) haemodilution, and with hydroxyethyl starch (HES) at 30 and 60% dilution. Other authors, such as Ng and Lo, also confirm these findings of hypercoagulability as judged by TEG[6] *in vivo*, while Janvrin[7] and Heather[8] reported an increased risk of perioperative deep venous thrombosis with crystalloid administration. Gelatins have had more of an equivocal track record with regard to coagulability. The results fall into categories ranging form hyper- to hypo-, or even no changes in coagulability. The HES group of fluids and the dextrans are well known to have inhibitory effects on factor VIII, thereby influencing platelet function.[9] What is interesting with HES is that even the starches can cause a faster clot initiation time (r-time), but with a reduced maximum amplitude at mild to moderate dilutions.

The Karoutsos[10] paper referred to by Gorton has also been incorrectly cited as showing no change. Karoutsos, in fact, showed no change in TEG variables in the albumin and HES groups in his study, but did find a significant shortening in r times and r+k times, coupled with significantly raised α angles in the gelatin group. These reflect a state of hypercoagulability The clinical picture, however, was no different.

Mardel[11] and colleagues only studied various measures of total clot strength in their study referred to by Gorton. This report failed to mention r times, k times, or α angles. Their work with gelatins was also compared with saline and Ringer's solution as control fluids. We have shown that crystalloids are inappropriate as controls, but should rather be seen as separate study fluids. The only appropriate control is fresh whole blood, undiluted.

Knowing the degree of haemodilution is essential in comparing data. Vast differences in TEG variables are found at different dilutions. A recent collaborative dose–response study at our centre (unpublished), with a novel HES in a balanced electrolyte solution, for example, revealed no significant decrease in r-times at 20%, but only at 30% haemodilution. The r-time returned to baseline at 50 and 60% dilutions. A similar picture was found with the k-times. A current dose–response study using saline is showing similar results, with 10% dilution showing almost no effect, but successive dilutions of 20–40% producing increasing coagulation.

Questioning the validity of the preferential dilution of circulating anticoagulants, e.g. antithrombin III (ATIII), is unsubstantiated by anything in this paper. Haemodilutions *per se*, with both crystalloids and colloids, leads to a *greater* fall in ATIII and fibrinogen than that which could be expected from the percentage haemodilution alone.[3] These authors have chosen to ignore the fact that we performed a controlled trial, in which we showed that crystalloid dilution produced a significant increase in the coagulation status of our conscious volunteers over a period of an hour, whereas haemodilution with starch solution had almost no effect on the TEG apart from a reduction in the MA (the opposite effect to that seen with crystalloid). Our study could not, therefore, have been merely a demonstration of environmental factors.

Gorton and colleagues have also given insufficient attention to a considerable body of work from a number of different centres that has consistently shown that *in vitro* 20–40% haemodilution with crystalloids (where environmental factors could have no effect) causes increased coagulation. In a study currently under consideration for publication, we have demonstrated that this effect can be inhibited by the addition of ATIII to the diluent fluid. To be as bold as to draw into question vast amounts of previous published work from several centres after one trial of minimal haemodilution with a single colloid intravenous fluid versus no fluid administration, we feel, is a bit naïve.

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Editor—Our study was part of an evaluation of thromboelastography (TEG) during Caesarean section. The only change of any significance was the one we reported. When we presented earlier work at an international meeting, we were advised from the floor that we would be naïve to attribute the changes we found to the gelatin infusion. Our study was prompted by this remark.

We are sorry if our summaries of the previously published work are too simplistic. To support our argument all that is necessary is that a difference exists between the *in vivo* and the *in vitro* findings, and that the *in vivo* findings are variable. We believe this to be the case. Tobias and colleagues[1] showed hypocoagulability at 11% haemodilution with colloid in their *in vitro* study, and we acknowledge that many studies dilute to 20% or more. The cannula for the second sample was inserted immediately before sampling and no fluid was infused.

In our discussion, we questioned the role of what we termed environmental factors in interpreting the changes detected. While we speculated on the role of stress, we have no doubt that there is more going on than we understand. Undoubtedly, cannula artefact can influence results, but we have failed to find any description of this in our searches. We do not maintain that TEG changes after intravenous infusion should never be attributed either to haemodilution or the fluid itself. Nor do we maintain that the phenomenon we describe is applicable to every study. The argument revolves around the role of artefacts, and we wish to point out that very few studies give sufficient details of sampling to make a judgement, and almost never is the possibility of artefact considered in the discussion. Our simple study raises issues that have not been adequately dealt with to date. There are a great many facts and too few explanations, and we believe a degree of scepticism can be accommodated. We hope that the studies in progress will shed more light and we look forward to reading them.

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1 Tobias MD, Wambold D, Galli K, Greer F. Haemodilution with saline albumin and hetastarch exert differential effects upon whole blood coagulation. *Anesthesiology* 1996; **85**: A225

Epidural top-ups solutions for emergency Caesarean section

Editor—In their interesting paper on preparation times for epidural top-up solutions, Lucas and colleagues refer to concerns about the stability of local anaesthetic mixtures prepared in advance.[1]

Chemical stability studies conducted by Robinson and colleagues confirmed that mixtures of 0.5% bupivacaine and 2% lidocaine, with the addition of either 8.4% sodium bicarbonate *or* 1:200 000 epinephrine, remain stable at room temperature for up to 24 h.[2] When sodium bicarbonate and epinephrine are *combined* in local anaesthetic solution, however, the alkalinization renders the epinephrine highly unstable resulting in its rapid degradation.

Those who favour a combination of local anaesthetics with additives for emergency epidural top-ups may therefore find it convenient to prepare their epidural mixtures in advance in a similar manner to the preparation of general anaesthesia drugs in obstetric anaesthesia. We believe that the advanced preparation of epidural local anaesthetic mixtures is safe provided epinephrine and bicarbonate are not combined.

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Postoperative orphenadrine withdrawal

Editor—A 56-yr-old woman with familial adenomatous polyposis, athetoid cerebral palsy and learning disability underwent elective subtotal colectomy and ileo-rectal anastomosis. Eleven days later, she underwent laparotomy for repair of anastomotic dehiscence and was admitted to the intensive care unit (ICU) postoperatively with sepsis. She required fluid resuscitation, antibiotics, inotropic and ventilatory support and was sedated with propofol and morphine until the third postoperative day. No neuromuscular blocking drugs were given. Though eye opening soon became spontaneous, her motor response remained minimal and she failed a trial of early extubation. Percutaneous tracheostomy was performed on day 5 and Glasgow Coma Scale (GCS) motor score varied between 1 and 3 over the next 3 days, but without progressive improvement. Her pupils were equal and reactive to light, and 2–3 mm diameter. Computed tomography (CT) scan of her brain was normal, and she was reviewed by a neurologist, who suggested that her slow neurological recovery could be ascribed to possible hypoxic or hypotensive encephalopathy sustained prior to laparotomy on a background of cerebral palsy.

Her GCS following her first operation was 15 and her only regular medication was orphenadrine 50 mg t.d.s. as long-term therapy for her cerebral palsy-related dystonia. Neurological examination revealed increased limb tone with resting tremor but normal power and reflexes, and no cranial nerve deficits. Orphenadrine was continued until her laparotomy, but stopped on the ICU. Orphenadrine was re-commenced via nasogastric tube on day 8 after a case report of trihexyphenidyl withdrawal encephalopathy was reviewed by the ICU pharmacist.[1] Neurological status improved over the next 2 days to a GCS motor score of 6 and the patient was discharged to the ward on day 11. Her pupils continued to be equal and reactive to light and were 3 mm in diameter. No changes in tremor or muscle tone were noted compared to her preoperative state.

Orphenadrine was continued but the patient required re-admission to the ICU 3 days later for ventilatory support following right basal lung collapse. Sedation with propofol and fentanyl was given for 14 h and the patient became fully responsive less than 4 h after sedation was stopped. She was discharged from ICU after 3 days and from hospital, 3 weeks later. At neurological follow-up after 2 months, CT scan was normal and while spasticity remained at pre-operative levels, no new or focal symptoms or signs were evident.

Orphenadrine is a muscarinic, cholinergic receptor antagonist with similar pharmacodynamic properties to other 'antimuscarinic' drugs like trihexyphenidyl (Benzhexol) and procyclidine, and may be used to treat tremor and rigidity in a range of movement disorders including parkinsonism. The British National Formulary suggests (under cautions) avoidance of abrupt discontinuation of treatment for all of these drugs.[2] Johkura and colleagues described trihexyphenidyl withdrawal encephalopathy in a 61-yr-old woman with mild Parkinson's disease who became comatose.[1] It was associated with miosis and slow wave electroencephalogram (EEG) activity on stopping medication but recovered over several days on reintroduction of the drug. A further trial of withdrawal led to a stuporous state which again resolved on recommencing therapy.

Our patient's GCS from day 3 to 8 on the ICU showed a striking reduction in motor score compared to her eye opening which was spontaneous. Her recovery from the second period of sedation, when she was receiving orphenadrine, was as we would have predicted. While numerous factors including three days of sedation, the use of morphine and the presence of sepsis may have contributed to delayed recovery during her first admission to ICU, the dominantly motor features of this delay, and the rapid response to reinstitution of orphenadrine following a plateau in her progress neurologically, lead us to suspect that orphenadrine contributed significantly to recovery. Our case is not as convincing as that of Johkura and colleagues, with no pupillary changes nor EEG information available. However, we suspect that our experience may be the first case report of a comparable withdrawal syndrome after orphenadrine.

Abrupt withdrawal of antimuscarinic drugs has been associated with neuroleptic malignant syndrome,[3 4] and exacerbation of extrapyramidal symptoms,[5] including life-threatening cranial dystonia.[6] Use of these drugs has led to a central anticholinergic syndrome with reduction in GCS and mydriasis.[3] The effects of these drugs, both when commencing therapy and with abrupt withdrawal, can clearly be unpredictable and potentially dangerous.

We would suggest that for patients on long-term antimuscarinic therapy, administration should continue throughout the perioperative period unless there is a specific reason to discontinue it. Whilst in our patient the enteral route was established by the time we commenced therapy, switching to a parenteral preparation (e.g. benztropine or procyclidine) might be advisable when gastrointestinal absorption is unreliable.

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1 Johkura K, Matsumoto S, Hasegawa O, Kuroiwa Y. Trihexyphenidyl withdrawal encephalopathy. *Ann Neurol* 1997; **41**: 133–4
2 British National Formulary, Sept 1999; 38: 233
3 Guze BH, Baxter LR Jr. Current concepts. Neuroleptic malignant syndrome. *N Engl J Med* 1985; **313**: 163–6
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5 McInnis M, Petursson H. Withdrawal of trihexyphenidyl. *Acta Psychiatr Scand* 1985; **71**: 297–303
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Protecting anaesthetic tubing from occlusion: an inbuilt solution

Editor—We are indeed 'frustrated' with the limited mobility of modern anaesthetic machines, when the wheels become 'chocked' by pipelines, electrical cables and similar structures. Dell and Cochrane[1] describe an ingenious solution to this problem that may have prevented the back pressure due to compression of the scavenging system which was described by Dr Carvalho.[2] However, the need for this home-made system would be negated if manufacturers of anaesthetic machines were prepared to attach the system built into the wheels of a number of portable x-ray machines. These avoid being 'chocked' by including four vertical prongs into the hub of each wheel. They protrude almost to floor level: a pair on either side of the leading edge of each wheel (Figure 1). We feel these could be made of a material suitable to meet antistatic or other technical requirements and would ensure that anaesthetic machines could easily be moved without the risk of tube compression.

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1 Dell R, Cochrane D. Protecting anaesthetic tubing from occlusion. *Br J Anaesth* 2000; **84**: 698
2 Carvalho B. Hidden hazards of scavenging. *Br J Anaesth* 1999; **83**: 532–3

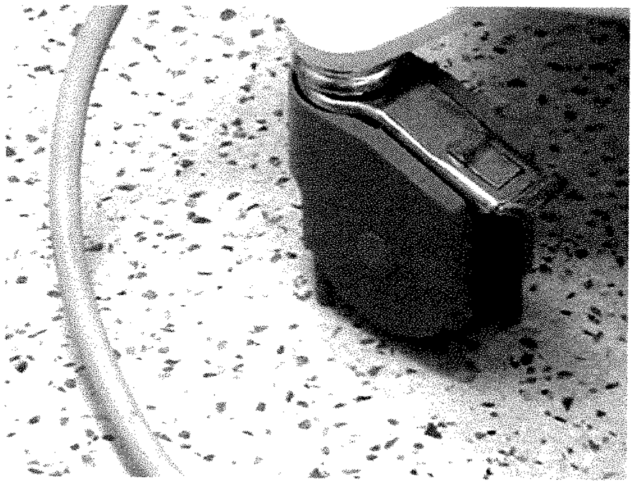

Fig 1 Two pairs of vertical prongs attached to the margins of the hub prevent tubing 'chocking' the wheels.

Headaches in the prenatal period

Editor—Two recent case reports have highlighted the need to consider alternative pathology when presented with a patient complaining of headaches in the postpartum period.[1 2] In both cases the situation was complicated by the patients suffering accidental dural puncture during epidural catheter insertion. The differential diagnoses and the management of the pathology were described.

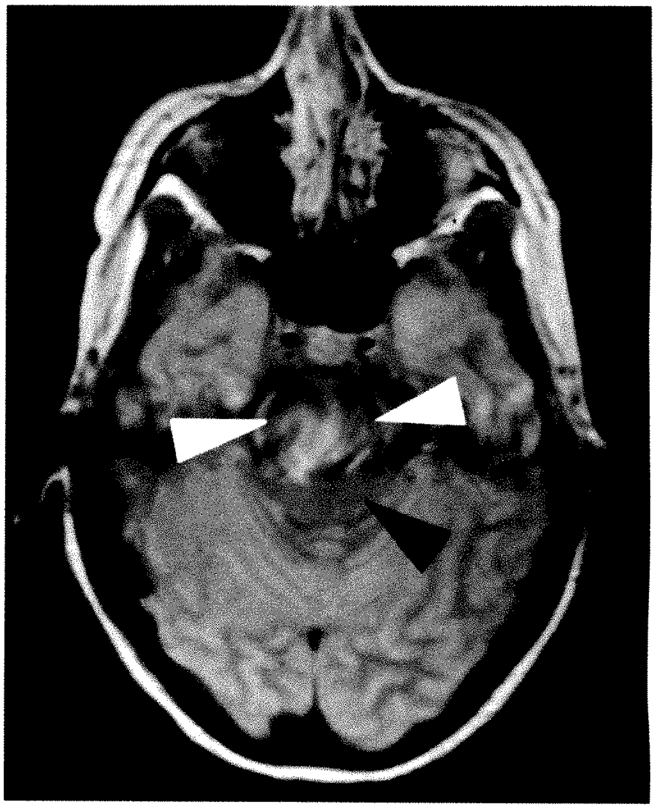

Fig 1 MR scan of the brain showing a large rounded mass in the pre-pontine region measuring 3.5 cm in its maximum diameter (light arrows). There is associated severe compression of the pons and mid brain (dark arrow).

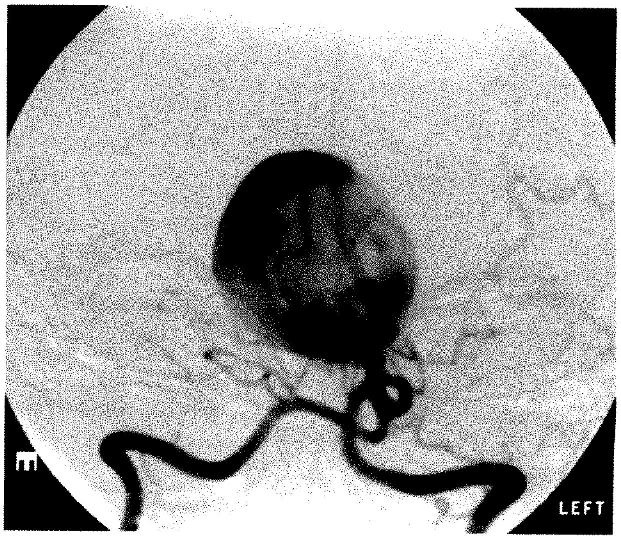

Fig 2 Cerebral angiography with digital subtraction showing a giant basilar tip aneurysm.

Headaches are not uncommon in the prenatal period and I wish to illustrate this with a recent case that presented on our emergency list. The obstetric and neurosurgical management is described.

A previously healthy 28-yr-old multiparous woman presented at 36 weeks gestation with a 6-week history of frontal headaches. She was known to experience the occasional migraine attack. A diagnosis of sinusitis was made and she was reassured and discharged home. Two weeks later she was admitted from the antenatal clinic with similar frontal headaches which tended to be worse in the mornings and which were exacerbated by coughing and sneezing. She had not experienced any fits, faints or blackouts. A diagnosis of tension headaches was made and she was treated with simple analgesics. The next day the headache was no better and a CT scan was performed. This revealed a large enhancing mass arising in the region of the clivus and extending upwards with compression of the pons (Fig. 1). There was associated mild dilatation of the third and lateral ventricles. The differential diagnosis was either meningioma or cerebral aneurysm. The patient was listed for a Caesarean section and insertion of an external ventricular drain. After much deliberation it was felt that performing either the obstetric or neurosurgical procedure first did not convey any significant advantage.

In the operating theatre, a 14G intravenous cannula and 20G radial arterial cannula were inserted. Following preoxygenation, we gave a bolus dose of remifentanil 1.5 μg kg^{-1} followed by thiopental 400 mg and rocuronium 50 mg. Cricoid pressure was applied from loss of consciousness until the trachea was intubated. Anaesthesia was maintained with isoflurane (end-tidal concentration 0.5–1.0%) in an oxygen/nitrous oxide mixture, and the remifentanil was continued as an infusion at a rate of 0.05–0.15 μg kg^{-1} min^{-1}.

The Caesarean section was uneventful with minimal blood loss. The baby was blue and floppy at birth with a heart rate of 60 beats min^{-1}. The heart rate increased to 100 beats min^{-1} with supplemental oxygen and ventilatory support with an Ambu bag and mask. The baby's trachea was intubated. Naloxone 200 μg i.m. was given at 2 min The baby's colour improved, regular breathing ensued and the tracheal tube was subsequently removed. The Apgar scores were 4 at 1 min, 7 at 5 min, and 10 at 8 min.

Insertion of a frontal external ventricular drain was also completed without problems. Throughout surgery the heart rate varied between 60 and 80 beats min^{-1}, and the systolic blood pressure remained at 110–140 mm Hg. Morphine 10 mg was given at the end of surgery. Following extubation, labetalol 10 mg was given to reduce the blood pressure to normal limits. Both mother and neonate made an uneventful recovery.

We are always taught that 'common things are common'. In our patient, the initial impression was sinusitis and then tension headache. There were no other features of a more serious cause of persistent headaches such as pregnancy-induced hypertension, meningitis, or subarachnoid haemorrhage. It was the failure of the headache to improve that prompted the request for a CT scan

At the time of surgery, the exact nature of the intracranial mass was unknown. We assumed it to be a vascular lesion. The use of remifentanil was associated with stable haemodynamics throughout anaesthesia. In a similar case, Bedard and colleagues[3] used remifentanil in a parturient with a large acoustic neuroma undergoing Caesarean section. They found no severe neonatal respiratory depression. A further study in 19 parturients[4] found that remifentanil crossed the placenta but appeared to be rapidly metabolized, redistributed, or both, and found no adverse effects on the neonates. But we can only assume that the reason for the profound neonatal depression in our case was the remifentanil

We believe the correct decision was made in performing the Caesarean section before the neurosurgical procedure In particular, it was felt that in the presence of a neurosurgical catastrophe, the situation would be less complicated if the baby was already delivered.

Subsequent investigations have confirmed the diagnosis of a basilar artery aneurysm (Fig. 2).

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Book Review

Anaesthetic Data Interpretation: Understanding Key Concepts for the FRCA. Sylva Dolenska. Published by Greenwich Medical Media, London. Pp. 176; illustrated. Price £19.50. ISBN 1-84110-0080.

Anaesthesia Data Interpretation is one of the Greenwich Medical Media series of soft covered handbooks that will be familiar to many anaesthetists. It adopts a graphical approach with illustrations facing the text on pairs of pages. As the author explains in her preface this approach is deliberate, since she believes that using illustrations is probably the best way of summarizing the amount of detailed information required by students for the FRCA. It is divided into five parts which in turn are divided into individual articles on single topics.

Part 1 covers physics, mathematics, statistics and anaesthetic apparatus The gas laws and the kinetics of gases are summarized with admirable brevity. In 12 pages of text she manages to explain turbulence, adiabatic and isothermal compression of gases and finish off with force, work and power, all worked from a basis of the kinetic theory of gases. The illustrations lead the text well and the explanations are clear and easy to follow. However, sometimes it takes time to see what the detail of the illustrations means and there is an irritating inconsistency of style in the illustrations that is repeated many times within the book. One of the other shortcomings, or maybe it is really an advantage, appears even in this early part. The title of the book suggests its intention is to convey concepts. However, the author often misses out the very link that would enable the reader to appreciate the concept she uses to give her explanation. For instance, whilst these early articles are based on kinetic theory of gases (i.e. the idea of representing gases as collections of flying billiard balls) she does not point this out. Although she is as good as her title in that she is not frightened of giving the mathematical explanation of an effect, the ultimate way of conveying concepts in the physical sciences, the book is more a set of good notes for an able student who already understands the concepts, than a way into the concepts themselves. Part 1 closes with statistical graphs and basic mathematical forms such as the straight line and the exponential and finally a description of two non-absorber breathing systems, the Mapleson A and the T-piece, and graphs describing the pressure flow characteristics of basic ventilators.

Part 2 is called clinical measurement but is really an examination of how physiology measurement instruments work and some consideration of what their output looks like. On page 80 we get the first piece of real data interpretation in the explanation of different capnograph traces. The author comes a bit unstuck trying to explain pulse oximetry starting from Beer-Lambert's Law, but then don't we all, though her explanation would get anyone through the examination. The next two parts are on physiology: Part 3a, Cardiovascular Physiology; and Part 3b, Respiratory Physiology. In these sections her earlier careful use of mathematics pays off, in that she can now explore the physiology using the knowledge that her readers have from the previous sections. The shortest part and the last, is on pharmacology.

On the credit side this book will encourage readers to think about the issues of how measurements are made and what they mean as they come across those problems in their practice. That really is the best way to become familiar with concepts. The layout will also encourage them to produce well-structured viva answers.

On the debit side this book misses a number of opportunities. There are few encouragements for self-assessment. The bibliography is unbelievably short and inadequate considering the number of texts on the basic sciences which the author could have indicated to the readers, including others in the same publisher's list.

I think this book would more aptly have been called *Notes on anaesthetic data interpretation*. Viewed in this light, at £19.50 this is a bargain set of excellent notes. It will be high on my list of recommendations to my Autumn FRCA course.

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British Journal of Anaesthesia **85** (3)· 500 (2000)

Erratum

Pulmonary hypoperfusion in cyanotic heart disease (BJA 2000; 85: 154P)

The keywords published with this abstract were incorrect. The appropriate keywords are given below. The publisher apologizes for this error.

Keywords: carbon dioxide, elimination; heart, congenital defects; haemoglobin, saturation

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Three to five key words or phrases (for indexing) should be included below the summary.

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2. Hull CJ. Opioid infusions for the management of postoperative pain. In. Smith G, Covino BG, eds. *Acute Pain* London Butterworths, 1985; 155–79

Monographs:

3 Moore, DC. *Regional Block*, 4th Edn Springfield, Illinois· Charles C Thomas, 1979

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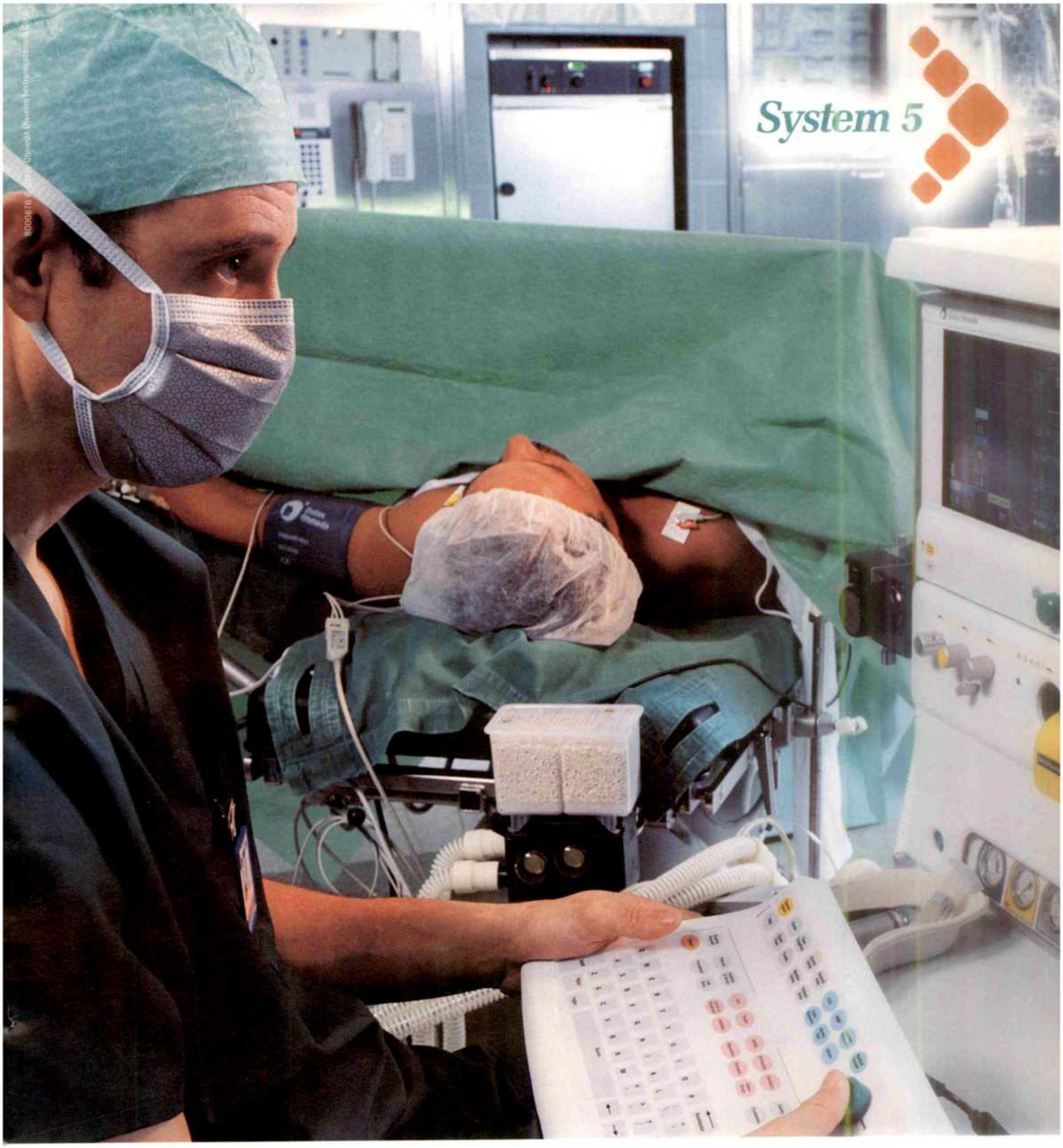

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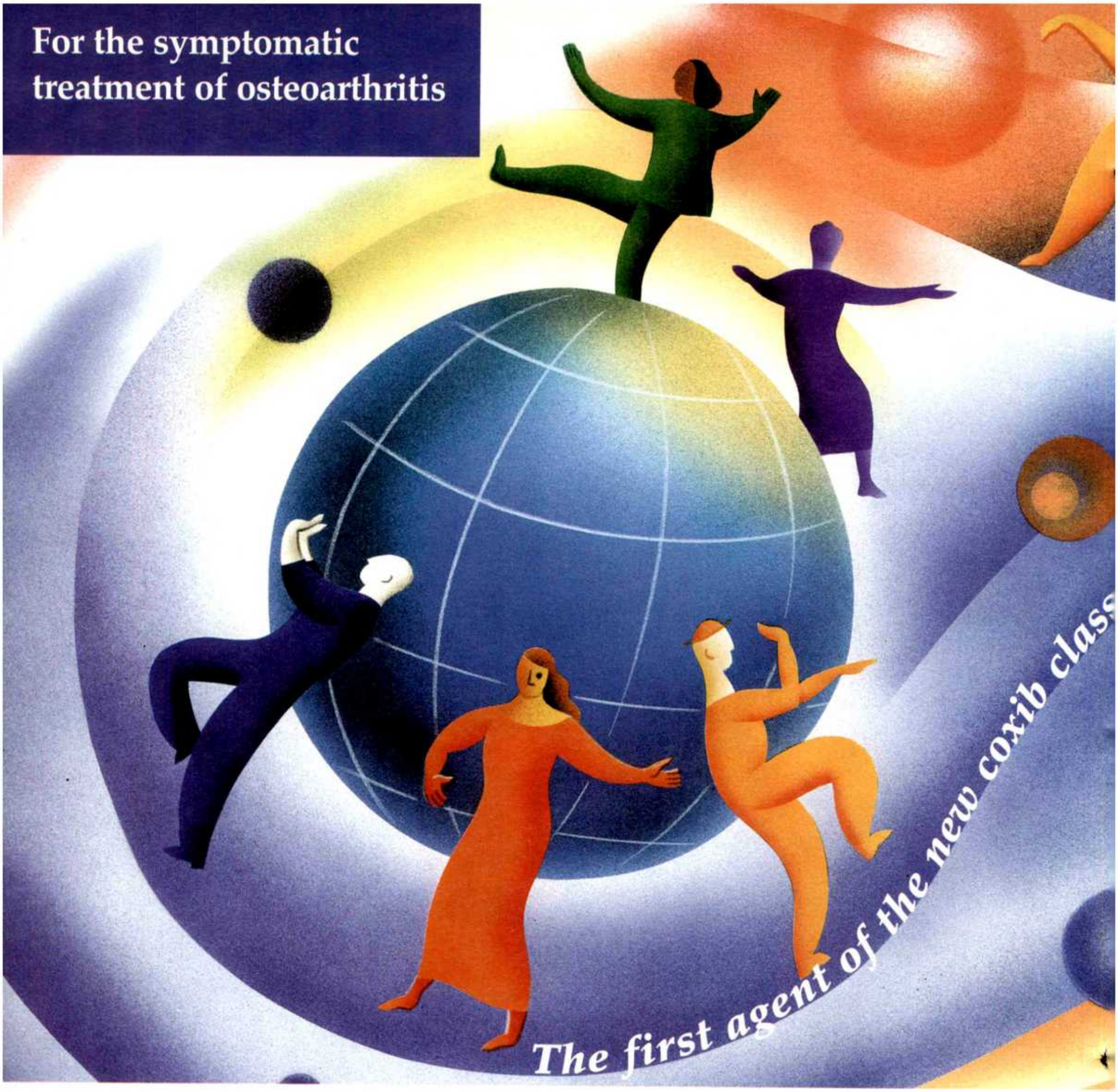
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The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

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Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

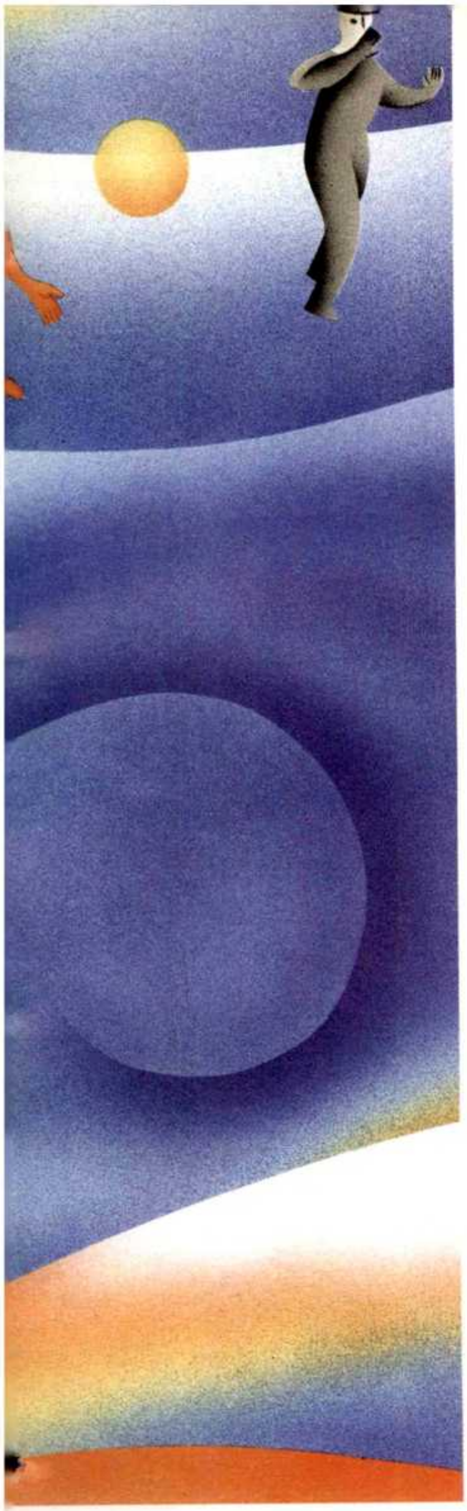
Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

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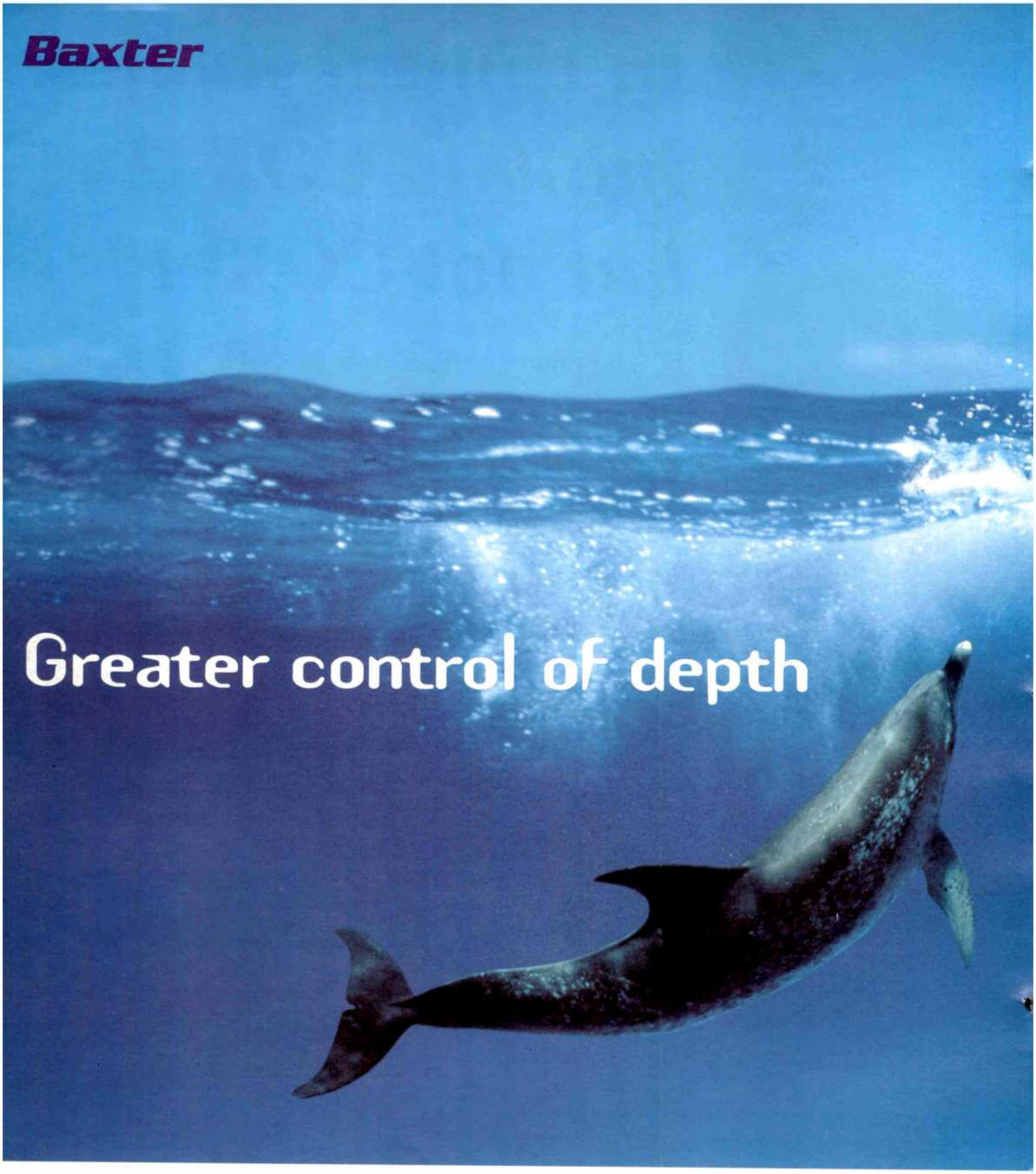

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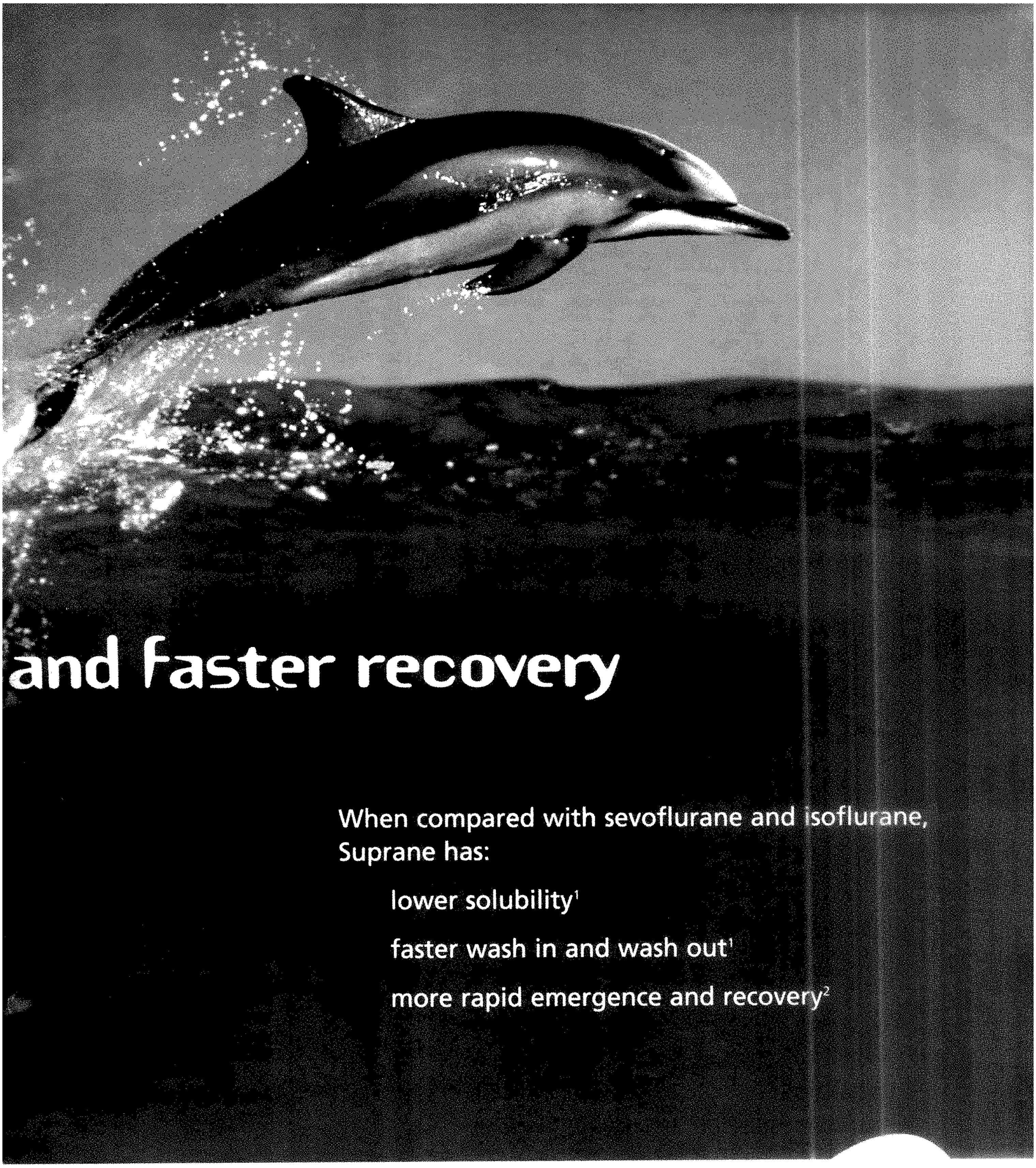
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faster wash in and wash out[1]
more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

® Denotes registered trademark.

References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

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UP021/UK/020

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Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK. (PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
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Earlier participation in rehabilitation[3]

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*Haemoglobin levels >10 to ≤13 g/dL.

References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

Please see abbreviated Prescribing Information on adjacent page.

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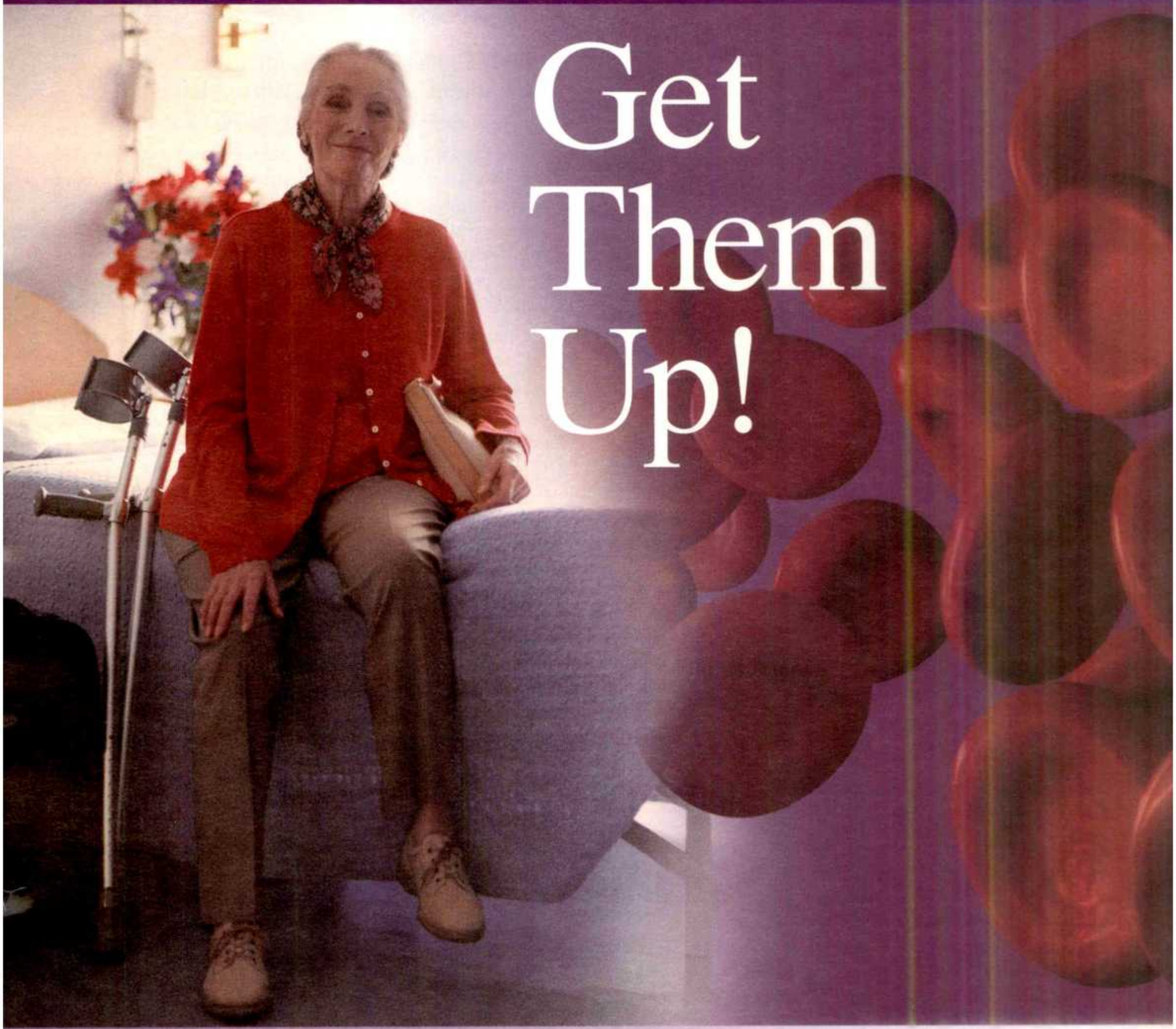

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Editorial Notices

BJA/RCA Research Fellowships

The *British Journal of Anaesthesia*, in conjunction with the *Royal College of Anaesthetists*, is making a further round of grants available to support research in anaesthesia, intensive care or pain relief. The work must be conducted in the United Kingdom.

Small project grants: Grants are available to support specific research projects in anaesthetic departments. Joint applications with basic science departments will be welcome. These grants may be awarded to fund technical staff, research students or post-dostoral research fellows, salaries, or items of equipment. The maximum value of any award will be £15 000, and the *BJA/RCA* will not contribute towards overheads.

The *BJA/RCS* will not be funding Research Fellowships or Full Project Grants with this round of awards; the aim of these applications is to provide support as 'pump-priming' monies for future more substantive applications.

For further details and forms, please **WRITE** or **e-mail** to:

Dr J. W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU *or* john.sear@nda.ox.ac.uk

Closing date for applications is **OCTOBER 11, 2000.** Late applications will **not** be considered.

Anaesthetic Research Society Grants 2000

The Anaesthetic Research Society is offering three grants in the present round.

Health Family Grant: two grants up to £4000 each.

Anaesthetic Research Society Millenium Grant: one grant of up to £12 000

Applicants must be members of the Anaesthetic Research Society in good standing. Grants will be administered within the United Kingdom. Applications will be considered for projects in the areas of anaesthesia, pain relief, intensive care medicine, and basic sciences related to these topics. The closing date is October 31, 2000. Further details and applications can be obtained from the grants officer: Dr M. C. Bellamy, Intensive Care Unit, St James's University Hospital, Leeds LS9 7TF, UK. Or electronically (preferred option) through ARSGrants@Livertransplant.org.uk

13th Annual Congress of the European Society of Intensive Care Medicine

Rome, Italy, October 1–4, 2000

For further information, please contact:

ESICM Congress Secretariat, 40 Avenue Joseph Wybran, B-1070 Brussels, Belgium.

Tel: + 32 2 559 0355; Fax: +32 2 527 0062; E-mail: public@esicm.org; Internet http://www.esicm.org

Dingle 2000 – Current Controversies in Anaesthesia and Perioperative Medicine

Dingle, County Kerry, Ireland, October 4–8, 2000

University College London Hospitals Centre for Anaesthesia announce a call for abstracts: there is an opportunity to submit work for poster presentation and selected finalists will be invited to give an oral presentation (prizes totalling £1000). Any research is acceptable provided it has not been published in any peer reviewed journal by the abstract deadline of 30 June 2000.

For further abstract and meeting registration details please contact:

Dr Monty Mythen, Centre for Anaesthesia, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK.

Tel: +44 20 7380 9477; Fax: +44 20 7580 6423;
E-mail: uch.acru@btinternet.com

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.

Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.

Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)

Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

Wood Library-Museum's Quadrennial Laureate of the History of Anesthesia Prize

Members of the Editorial team of the *BJA* are pleased to announce that, Dr Thomas B. Boulton (UK) and Dr Norman

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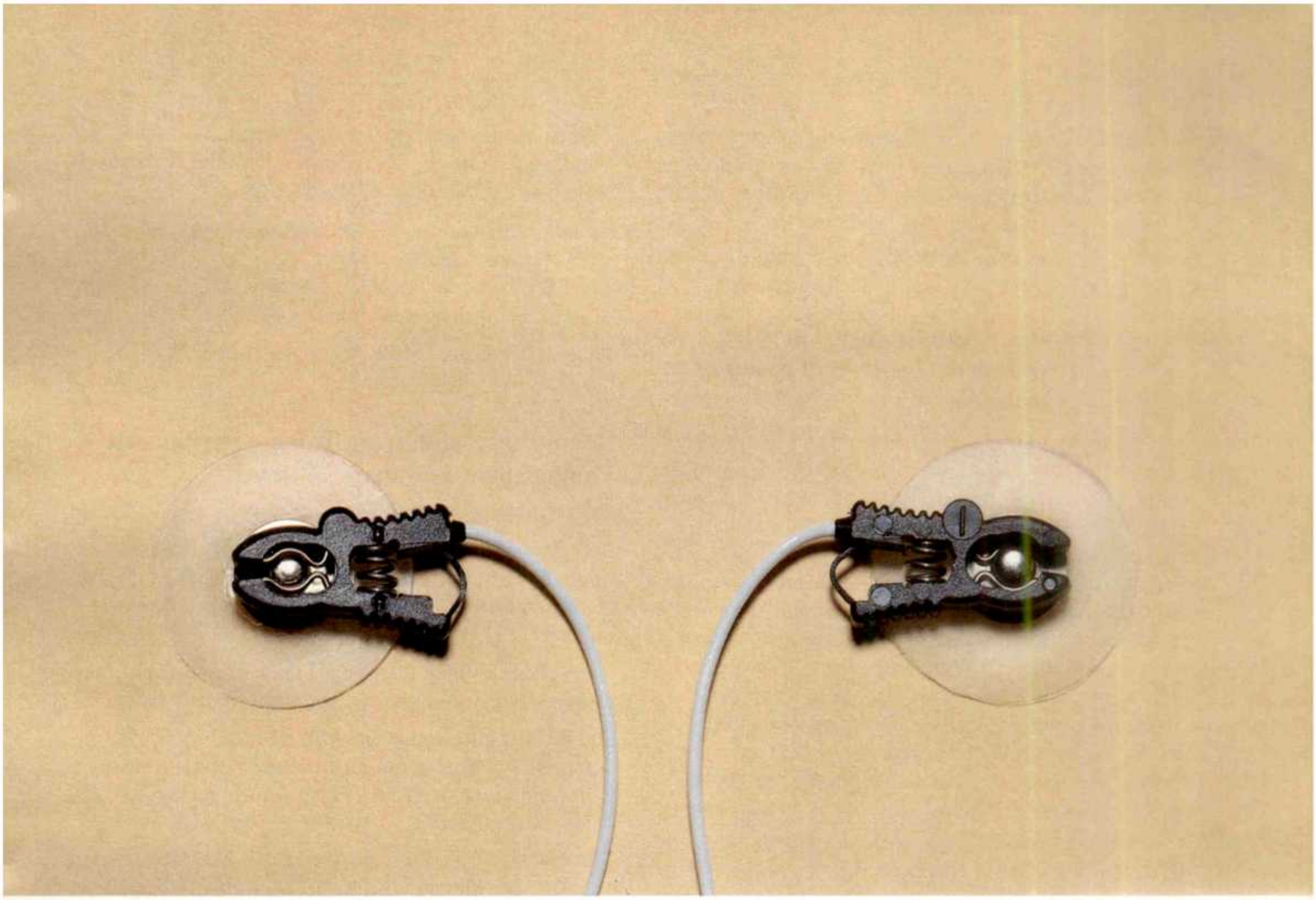

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A. Bergman (USA) are to be awarded the Wood Library – Museum's quadrennial Laureate of the History of Anesthesia Prize at the annual meeting of the American Society of Anesthesiologists in October 2000, in San Francisco.

We offer our hearty congratulations to Dr Boulton, and to the family of Dr Bergman, who unfortunately died recently.

Awareness during Anesthesia—The 2000 *Anesthesiology* Journal-sponsored Symposium at the ASA Meeting

San Francisco, California, October 17, 2000, 9:00–12:30

The moderators will be Alex S. Evers MD (Washington University, St Louis) and Richard B. Weiskopf MD (University of California, San Francisco)

Awareness during anaesthesia is a potential problem of concern to clinicians and the public. There are clear cases of patients having been unintentionally awake during anesthesia and surgery and other cases for which 'awareness' was not as clearly delineated. 'Awareness' during anaesthesia and surgery can result in 'post-traumatic stress syndrome'.

This symposium will include invited speakers and a discussion session, as well as an opportunity to view selected abstracts. Abstracts in the following areas are considered appropriate for submission:

(i) epidemiology of 'awareness' during anaesthesia,
(ii) monitoring of depth of anaesthesia,
(iii) prevention of awareness during anaesthesia,
(iv) treatment of syndromes resulting from awareness during anaesthesia.

Abstracts should be submitted via the regular Annual Meeting procedures by April 1, 2000. *Online submission is available.* Abstracts requesting consideration for presentation at this symposium will undergo an additional review in addition to the standard ASA abstract review process. If you would specifically like your abstract considered for inclusion in the symposium, please check the special box that can be found on the cover letter/form which must accompany your submission. If you need abstract submission materials, please contact the American Society of Anesthesiologists:

American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068–2573, USA.

Tel: +1 847 825 5586; Fax: +1 847 825 1692;
E-mail: mail@ASAhq.org Web site: http://www.asahq.org

3rd SW Thames Anaesthesia Forum

Da Balaia, The Algarve, Portugal, October 23–26, 2000

The scientific programme will includes lectures and discussions on: Acute and Chronic Pain; Paediatric Update; Obstetric Anaesthesia; Neurology and Anaesthesia; ITU and Relevant Medical Topics; Cardiothoracic Anaesthesia; Day Case Surgery; Regional Blocks; New Drugs Update; Training and Education; Information Technology; Free Papers. Guest Speakers, Workshops, Videos on new Drugs, Equipment and Techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: September 1st. Meeting approved for CME.

For full information and for on-line registration please visit: www.anaesthesiaupdates.com
Dr J.B.Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT.

Tel: +44(0) 20 8275 0018; Fax: +44(0) 20 8725 3135;
Email: liban@mailbox.co.uk

Haemostasis and Transfusion—Perioperative Management in Elderly Patients

Graz, Austria, October 27 and 28, 2000

This symposium has been organized by the Department of Anaesthesiology and Intensive Care Medicine, University of Graz and Department of Anaesthesiology, University of Munich.

The preliminary programme includes: haemostasis and transfusion, and perioperative management in elderly patients.

For further information contact: M. Neuray/G. Taucher, Department of Anaesthesiology and Intensive Care Medicine, LKH-Universitätskinikum Graz, Auenbruggerplatz 29, A-8036 Graz, Austria.

Tel: +43 316 385 3027; Fax: +43 316 385 4664; E-mail: haemostasis@kfunigraz.ac.at. www.kfunigraz.ac.at/uanwww/haemostasis.htm

Resuscitation Fluids: Update 2000

Institute of Electrical Engineers, London, UK, November 17, 2000

Organised by the Centre for Anaesthesia, Royal Free and University College Medical School (RFUCMS), London, UK and The National Hospital, University of Oslo, Norway. This meeting has an internationally renowned faculty who will be cross examined by a panel of experts on topics including: Is albumin dead? Haemoglobin: How low can you go? Abnormal saline; The ideal colloid; Hyperoncotic/hyperosmolar; Risks of blood transfusion – oxygen carrying solutions.

Immediately following the meeting there will be a twilight trip to the 'London Eye' for all interested parties.

For further details please contact: Dr Monty Mythen, Centre for Anaesthesia RFUCMS, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London W1N 8AA, UK.

Tel: +44 (0)20 7380 9477; Fax: +44 (0)20 7580 6423;
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Royal Albert Hall, London, UK, November 21, 2000

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11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

5th International Conference on Memory, Awareness and Consciousness – Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, USA, June 1–3, 2001

This conference builds on the tradition of the previous Memory and Awareness in Anesthesia Conferences, and will focus on the following topics: measurement and monitoring of memory function, awareness and consciousness; interaction of anesthetic and sedative drugs with the mechanisms of consciousness, awareness and memory processes; consequences and treatment of unwanted awareness or memory function during surgery or critical care; impact of surgery, anesthesia and critical care on cognitive and psychological processes; neuroimaging and mapping of consciousness, memory, awareness and pharmacologic effects on them in the CNS.

Deadline for abstracts: December 10, 2000.

For further information contact us via e-mail at mac@mskcc.org or visit our web site www.maacc.org or by mail: Ruth Reinsel, PhD, Dept of Anesthesiology/CCM, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10021, USA.

Tel: +1 212 639 6038; Fax: +1 212 772 8646.

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

Free Papers will be accepted for oral and poster presentation in four categories: (i) monitoring; (ii) new pharmacological agents; (iii) interesting case reports; (iv) cardiopulmonary bypass technology. Abstracts forms are available upon request. The deadline for submission is November 1, 2000. Tuition will not be waived. Brochure available in June 2000.

For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

Association of Cardiothoracic Anaesthetists

Symposium on Cardiopulmonary Transplantation
Newcastle upon Tyne, UK, February 1, 2001

Topics include: (i) Management of end-stage respiratory failure; (ii) Mechanical support for the failing heart; (iii) Cardiac transplantation; (iv) Cardiopulmonary transplantation in children; and (v) Re-perfusion injury.

For further information and registration details please contact: Dr S. R. Haynes, Department of Cardiothoracic Anaesthesia, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN, UK.

Tel: +44 (0) 191 2843111, ext: 26488; Fax: +44 (0) 191 2231175; E-mail: judith.iley@nuth.northy.nhs.uk

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)
Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

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16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail: akabogu@mcn-nuernberg.de; www: http://www. mcn-nuernberg.de

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.

Tel: +49 911 393160; Fax: +49 911 331204

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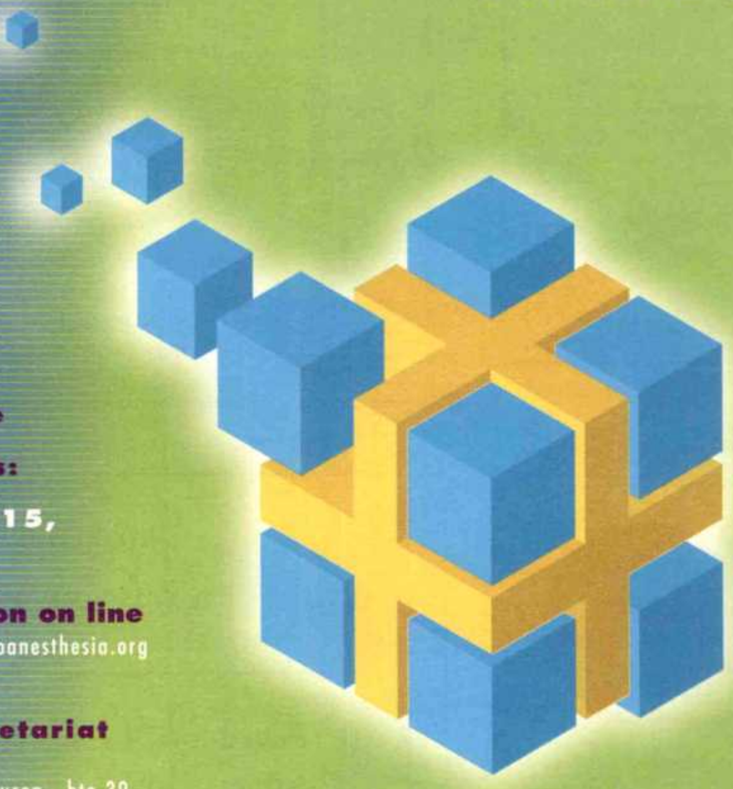
9th ESA Annual Meeting Gothenburg

APRIL 7-10 2001



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CENSA

In cooperation with the European Academy of Anaesthesiology

South West Thames Anaesthesia Updates

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3rd SW Thames Anaesthesia Forum
23-26 October 2000
Da Balaia, The Algarve, Portugal

12th SW Thames Anaesthesia Update
22-26 Janaury, 2001
Belle Plagne, French Alps

The Scientific Programme will include lectures, and discussions on:

- Acute and Chronic Pain
- Paediatric Update
- Day Case Anaesthesia
- Obstetric Anaesthesia
- Neurology and Anaesthesia
- ITU and Relevant Medical Topics
- Cardiothoracic topics
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RESUSCITATION FLUIDS: UPDATE 2000

Institute of Electrical Engineers,
London, UK ~ 17th November 2000

Organised by Centre for Anaesthesia, Royal Free and University College Medical School, London, UK and National Hospital, University of Oslo, Norway. The meeting has an internationally renowned faculty who will be cross-examined by a panel of experts on topics including:

• Is Albumin dead? • Haemoglobin: how low can you go?
• The ideal colloid. • Abnormal saline.
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For a full programme and details of sponsored places for professionals with a specialist interest in Resuscitation Fluids please contact Dr Monty Mythen:

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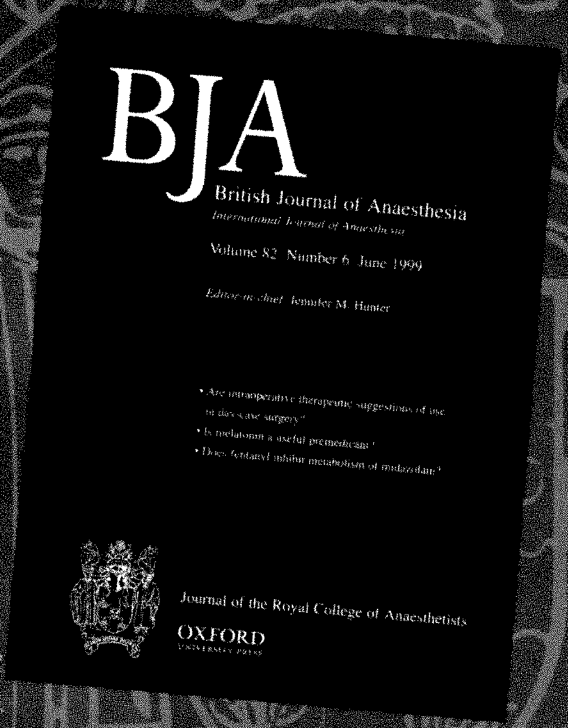
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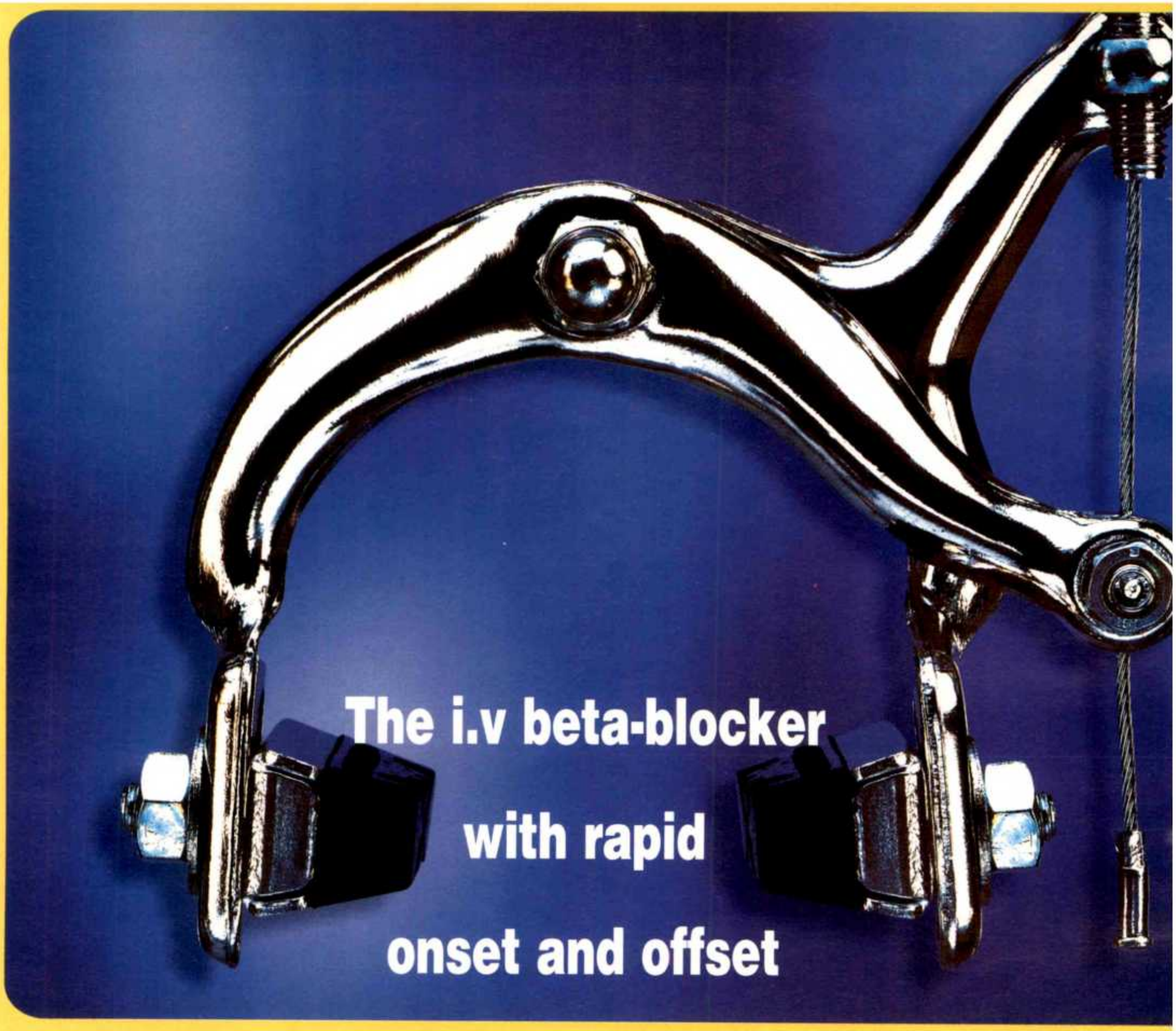

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Editorial I

The utility of pulmonary artery catheterization

Some of the most fascinating aspects of intensive care medicine are the controversies about patient management. A paradigm is the utility of the pulmonary artery catheter. Its use has been a matter of contention, more so since a paper by Connors and co-workers in 1996.[1] This study of patients in a group of American teaching hospitals demonstrated an association between the use of pulmonary artery catheters in the first 24 h of intensive care and increased mortality. During the subsequent discussion, there were calls for a moratorium on the use of the pulmonary artery catheter and, more constructively, for randomized controlled trials to examine patient outcome after use of the device.[2]

In this issue of the journal, a study of apparently similar design to the Connors' paper describes very different findings and will renew the flames of this debate.[3] Before discussing these contrasting works, let us consider how to evaluate diagnostic and monitoring devices. I have used the framework described by Guyatt and colleagues[4] (Table 1).

(1) Technological capability

Pulmonary artery catheters measure juxta-cardiac pressures, cardiac output and mixed venous oxygen saturation. Modern pressure transducers perform well in terms of their physical characteristics. However, the limitations of juxta-cardiac pressures in the clinical assessment of cardiac pre-load must be considered, and has been cogently discussed elsewhere.[5]

Thermodilution and Fick-derived cardiac outputs have been compared with varied results. Some studies demonstrated that thermodilution cardiac outputs were consistently less than those determined by the Fick method in low-flow states.[6] This may be a result of heat transfer to the injectate during its passage down the catheter. The accuracy of the thermodilution system may be improved by the use of dual thermistors.[7] The accuracy of continuous pulmonary arterial oxygen saturations has been confirmed by comparison with oximetric analysis of mixed venous blood samples.[8]

(2) Range of possible uses

Consensus statements from Europe and America have defined several situations in which the pulmonary artery catheter may provide useful information.[9 10]

(3) Diagnostic accuracy

Several observational studies have shown that data derived from pulmonary artery catheterization are poorly predicted by clinical skills alone.[11–13] For example, Connors and colleagues[11] showed that pulmonary artery pressures and cardiac outputs of critically ill patients were only correctly predicted on ~ 40% of occasions, and concluded that pulmonary artery catheterization 'results in a more accurate haemodynamic assessment'. Furthermore, doctors' abilities to interpret haemodynamic data are incomplete,[15 16] and it is worrying that the potential for such information to complement clinical findings may not be realised.

(4) Therapeutic impact

Therapeutic decisions are altered because of the data derived from pulmonary artery catheterization after 40–60% of insertions.[11–14]

(5) Patient outcome

The ultimate patient outcome is survival to a reasonable lifestyle. But the assessment of the impact of a monitoring tool on survival is fraught with difficulties. Even if the device performs adequately, providing clinically relevant information which is interpreted correctly by the clinical team who invoke changes in patient treatment, it is by no means certain that any therapeutic regimen manipulating haemodynamic variables improves patient survival. While supra-normalization of oxygen transport, using data derived from a pulmonary artery catheter, may improve survival of patients with significant co-morbidity undergoing major elective surgery,[17 18] this tactic does not improve survival of

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Table 1 Framework for clinical evaluation of diagnostic technologies[4]

(1)	Technological capability	Has the ability of the test to perform to specifications been determined?
(2)	Range of possible uses	Does the technology promise to provide information in a number of clinical situations?
(3)	Diagnostic accuracy	Does the technology provide information that allows health care workers to make a more accurate assessment of disease?
(4)	Therapeutic impact	Are therapeutic decisions made by health care providers altered as a result of the application of the test?
(5)	Patient outcome	Does the application of the technology result in patient benefit?

all-comers to intensive care[19] and may even increase mortality.[20]

Survival from critical illness also depends on many other factors which will confound studies of this complex process. The two studies mentioned at the start have attempted to examine patient outcome after a period of critical illness during which the patients may have undergone pulmonary artery catheterization. By using a 'propensity score' they have attempted to adjust for potential confounders, which may influence both the likelihood of pulmonary catheterization and the chance of death.

Murdoch and colleagues[3] examined the effect of pulmonary artery catheterization at any time on mortality in all patients admitted to a large intensive care unit in an English teaching hospital over a 7-yr period. Using stepwise logistic regression analysis, they devised a score of the propensity for pulmonary artery catheter insertion during the entire intensive care period. This propensity score was then used to account for the patients' severity of illness in an analysis of use of the pulmonary artery catheter and intensive care mortality. In contrast to the case-matched Connors study,[1] there was no increased mortality associated with the use of pulmonary artery catheters.

Why was there such a difference in the findings of two, apparently similar, studies? It may be that the propensity score used by Connors and colleagues[1] did not adequately model the patients' severity of illness. These authors calculated that a missing covariable would have to increase the risk of death six times to explain the difference in mortality, and considered the possibility as unlikely. However, they did not consider the possibility of several missing covariables. Perhaps some of the different covariables used by Murdoch and colleagues[3] helped construct a more predictive model. These workers included important indices of severity of illness, such as presence of acute renal failure[21] and physician's prediction of outcome.[22] They also considered concomitant treatments not included by Connors, for example use of vasoactive drugs and the need for artificial ventilation.

As discussed by Murdoch, Connors and co-workers constructed a propensity score more relevant to a patient's condition on the first day of intensive care, while they used variables pertaining to the entirety of the intensive care stay. Thus, the propensity score used by Murdoch may have provided a better model for prediction of death following critical illness, so that the severity of disease and the process of intensive therapy explain the risk of mortality rather than the use of a monitoring device.

Cultural differences exist between American and British intensive care practice. An indicator of these differences is emphasized by the inclusion of years of education, income and type of medical cover as covariables in the propensity score of the Connors paper.[1] Indeed, patients managed with a pulmonary artery catheter were more likely to be male and to have medical insurance. Thus, the patients considered suitable for pulmonary artery catheterization in this study may be different from such British patients. If the patient groups were too dissimilar, it is not surprising that the findings of the studies were different. Vincent and colleagues[23] have suggested that medico-legal and even financial considerations may play a role in the inappropriate use of the pulmonary artery catheter.

The Connors study[1] took place in five intensive units. It has also been suggested by Vincent and colleagues[23] that the pulmonary artery catheters may have been used by physicians not specifically trained in intensive care. Observational studies have associated better patient outcome with management in closed units with intensive care-trained staff.[24]

The Connors study took place in 1989–1994, when the pursuit of supra-normal oxygen transport values was much in vogue. This therapeutic manoeuvre, which depends on pulmonary artery catheterization, has been demonstrated in one randomized controlled trial of 'all-comers' to intensive care to result in a higher mortality.[20] Thus, the therapeutic changes invoked by the data derived from pulmonary artery catheterization may have led to the higher mortality, as acknowledged in the discussion of Connors' paper. Therefore it is possible that differences in the use of haemodynamic data might explain the difference in the results of these two studies.

Given the difficulty in accounting for confounders in such cohort studies, there has been a clear need for randomized controlled trials into the utility of pulmonary artery catheterization. Such a trial was attempted in Canada, but interpretation was made impossible because of the high withdrawal rate of patients by their doctors and relatives resulting in a small sample size.[25]

However, the debate following the Connors paper[1] has led to the setting up of at least two randomized controlled trials into the utility of pulmonary artery catheterization in North America and Great Britain. Are such trials likely to determine a true effect of a monitoring tool on patient survival, given the complexity of critical illness? Murdoch and colleagues do not think so, and I too remain sceptical. The reasons why have to do with the difficulty in setting up a very large, rigorously conducted trial. Essential features should include clear standards for the indications for pulmonary artery catheterization, the subsequent care of catheters, and assurances that accurate data are obtained with optimal interpretation. More problematically, any invoked change of treatment would have to be standardized, according to the best available information.

Even if such a thorough protocol was adhered to in a large number of patients, I am also sceptical about the validity of survival as an outcome in a trial of a monitoring device. Many factors determine survival from intensive care, and will confound all but the truly large randomized controlled trial. Is it not more meaningful to use so-called 'surrogate markers' in an evaluation of a monitoring tool? These may include duration of the shock state, and the incidences and durations of acute renal failure and multiple organ failure. After all, it is these occurrences that we are trying to avoid in the critically ill by employing invasive haemodynamic monitoring to help optimize oxygen transport.

It is now over 30 yr since the introduction of bedside pulmonary artery catheterization, and the debate about its usefulness continues. Other technologies are being introduced to help assess cardiac performance in critical illness. It is not possible to discuss these methods in this editorial, but one of the lessons from the use and study of pulmonary artery catheterization is that we ought to assess the utility of these devices in a thorough, efficient manner.

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Conflict of interest

The author has received an educational grant from Baxter Healthcare plc

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Editorial II

Airway devices: where now and where to?

Since the advent of the laryngeal mask airway (LMA†), anaesthetists have become used to the advantages of 'hands-free' anaesthesia. Beforehand it was usual, when anaesthetizing spontaneously breathing patients, to maintain direct patient contact via the facemask used to deliver the anaesthetic gases. Trainees were taught the advantages of direct contact for continuous clinical assessment. By contrast, hands-free anaesthesia offered freedom of movement about the operating theatre, increased independence from assistants, and the opportunity to more readily monitor surgical activity. Over the same period, monitoring has become more sophisticated, but the cynic might suggest that the anaesthetist now needs to be hands-free to attend to monitor alarms. For anything other than minor cases, tracheal intubation was the order of the day as it provided the most secure airway and also mitigated against the risk of aspiration. Progressive exploration of the clinical applications of the LMA has gone on to challenge the need for intubation to protect the airway from aspiration.

In the last decade or so there has been a surge of interest in airway devices. While this may be seen to have been precipitated by the novelty of the LMA, this is not necessarily the whole explanation. Brain[1] has acknowledged the relevance of the introduction of propofol and its propensity for pharyngeal smooth muscle relaxation in substantially improving ease of use of the LMA. In a similar sense, the properties of the newer inhalation agents may also be important.[2] These changes were highlighted in McIntyre's review of historical airway devices[3] where he not only described the earlier devices but also recalled the context in which they were to be used (e.g. inhalation ether inductions). This early experience may explain why this problem received so little attention for a long period. The Shipway airway might now be seen as a forerunner of the COPA[4] in that both are oropharyngeal devices with a pharyngeal cuff and direct connection to the breathing circuit. By comparison, the concept of the laryngeal mask was itself entirely novel and described by the inventor as a 'face mask on the larynx' (i.e. the idea of the conventional face mask is applied directly over the laryngeal inlet).

The cuffed pharyngeal tube (CPT) described in this issue by Tashayod[5] may at first sight appear to be simply a foreshortened tracheal tube with a large pharyngeal cuff. The anteriorly eccentric nature of the cuff is clearly different from that of the COPA where the cuff is by comparison largely posterior. The latter feature has been commented on adversely as it tends to push the tip of the COPA into the tongue substance.[6] Non-symmetrical cuffs may not be entirely new, but presumably the technology for exploiting this option has tended to become more efficient with time. Another recently introduced device, the modestly named 'Airway Management Device' or 'AMD', has at the time of writing no clinical trials reporting its use.[7] At first sight this resembles the Combitube because it has two cuffs but just the one lumen. The lower cuff is designed to 'locate in the hypopharynx and assist in the positioning of the aperture opposite the laryngeal inlet' and its upper cuff is designed to elevate the tongue and epiglottis. The upper cuff is somewhat oval in shape and this is claimed to centralize the airway and account for hands-free usage. It is said to be a stable airway and easy to insert. Further clinical experience with both the CPT and AMD is eagerly awaited, but at present it is only the latter that has a CE mark.

In view of these recent changes, it is reasonable to again question what we might expect from an 'ideal airway device'. (Expectations have perhaps been increased by clinical experiences over the last decade and should not be expected to remain unchanged over the next.)

- Efficient conduit for pulmonary ventilation bypassing the upper airway.
- Easy, appropriate insertion even by non-specialists.
- Efficacy not drastically impaired by suboptimal placement.
- Stable in use once positioned (i.e. capable of 'hands-free' anaesthesia).
- Works equally well in abnormal as well as normal airways.
- Easily converted to tracheal tube placement (i.e. a 'dedicated airway').
- Good accept/reject profile (see below).
- Minimal/no aspiration risk.
- Easy sealing of the upper airway to allow intermittent positive pressure ventilation.
- Sealing should be with minimal pharyngeal distortion and/or distension.
- Cricoid pressure friendly.
- Negligible side effects profile.

It is suggested that of the above list at least half of the features noted are unlikely to have been seriously considered more than 10 yr ago. The term 'dedicated airway' describes devices which maintain airway patency 'while other major airway interventions are anticipated or in

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progress'.[6] It refers to devices which allow uninterrupted controlled ventilation while other measures are undertaken, such as converting from use of the device to tracheal intubation. Guedel airways, for example, would not come into this category. Other important and recently introduced devices may also not be 'dedicated' in this sense, but are advances in airway management and include protheses for sleep apnoea patients.[8 9] It is surprising that this class of airway advances so far seem to have had little impact on anaesthetic practice.

The 'accept/reject profile' is a notion advanced in Brain's writings on the development of the LMA.[1] It describes the relative potential for acceptance or rejection of a foreign body by the oropharynx. Rejection phenomena include excess coughing, secretion outpouring, retching and expulsion of the device. Obviously patient-specific factors are not irrelevant,[10 11] but equally some device shapes, constituent materials and designs will be better tolerated than others. It seems likely that we may not yet have discovered what makes for the most well-tolerated devices. Cuffs of tubes placed in the upper pharynx under local anaesthesia have been suggested to cause a swallowing reflex if dilation is too great or too fast.[6] Another aspect of the same idea might be the ability to retain an airway device under light sedation (or local anaesthesia) which then becomes rejected as the sedation decreases (or local wears off). The LMA is well tolerated during emergence from anaesthesia, but the ideal must be a device that is not only a good airway but also well tolerated in the awake subject, without the need for local anaesthesia. Paediatric anaesthetists might suggest that childrens' dummies have been used as airways in infants for many years to do just that.

The best alternative for the oesophagus/oropharynx interface is also far from clear. The options at present aim to minimize passive regurgitation (by being well tolerated) or try to produce a blocking effect with or without a tube acting as a vent. These alternatives may not be mutually exclusive. The application of cricoid pressure with any airway device may have implications which need to be considered.[12 13] It is interesting to speculate how, in the longer term, devices which terminate higher in the oropharynx than the LMA will compare as far as aspiration risk is concerned.

Overall, development of airway devices up to the present time can be considered to have been somewhat empirical. The understanding of the physiological dynamics of the oropharynx is limited and variations in pharyngeal anatomy may be greater than has been previously considered. This is clearly an important area for anaesthesia research and airway device design in the future.

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CLINICAL INVESTIGATIONS

Ropivacaine pharmacokinetics after caudal block in 1–8 year old children

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We studied the pharmacokinetics after caudal block of ropivacaine (2 mg ml^{-1}, 1 ml kg^{-1}) performed in 20 children aged 1–8 yr undergoing subumbilical surgery, in this open, non-comparative, multicentre study. Venous blood samples were collected up to 12–36 h. The mean (SD) peak plasma concentration, 0.47 (0.16) mg litre^{-1}, was achieved after 12–249 min. The free fraction was 5% and the highest individual peak plasma concentration of free ropivacaine was 0.04 mg litre^{-1}. Clearance was 7.4 (1.9) ml min^{-1} kg^{-1} and the terminal half-life 3.2 (0.8) h. Thus, the free plasma concentrations of ropivacaine were well below those associated with toxic symptoms in adults and the capacity to eliminate ropivacaine seems to be well developed in this age group. In this open study of 20 patients, ropivacaine was well tolerated and provided satisfactory postoperative pain relief without observable motor block.

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Ropivacaine, a local anaesthetic recently approved for use in adults, is less toxic to the central nervous system and heart[1] and interferes less with motor function[2] than bupivacaine. These characteristics of ropivacaine could potentially be of great benefit in the paediatric population, and preliminary results in children have shown ropivacaine to be as efficacious as bupivacaine.[3–5]

The primary aim of the present study was to investigate the pharmacokinetics of ropivacaine after caudal administration in children. A dose of 2 mg kg^{-1} was chosen on the basis of the experience of ropivacaine in adults and the doses of bupivacaine used in this age group. Secondary aims were to assess postoperative analgesia and motor block and to document any adverse reactions.

Materials and methods

The study was approved by local ethics committees. After obtaining written parental informed consent, 20 ASA I–II patients, aged 1–8 yr, weighing ≤25 kg and scheduled for elective surgery below the umbilicus, were enrolled in the study between October 1997 and September 1998. The patients were stratified into three age groups (1–2, 3–4 and 5–8 yr) with a minimum of five patients in each group. The study was performed according to Good Clinical Practice.

Anaesthesia

Patients were premedicated with midazolam rectally (0.3–0.45 mg kg^{-1}) or i.v. (0.1 mg kg^{-1}). Eutectic mixture of local anaesthetics (EMLA®, Astra Zeneca, Södertälje, Sweden) was used to prevent pain from the insertion of an intravenous catheter. Anaesthesia was induced by thiopentone 5–10 mg kg^{-1} i.v. and maintained by sevoflurane, nitrous oxide and oxygen. Airway management consisted of a face mask, laryngeal mask airway or endotracheal intubation, depending on the type of surgery and the expected duration of surgical intervention. For endotracheal

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intubation, adequate muscle relaxation was achieved by administration of atracurium 0.5 mg kg^{-1} i.v. or suxamethonium 2.0 mg kg^{-1} i.v. After induction of anaesthesia, a second intravenous cannula was inserted, for use for blood sampling only. The patient was then placed on their side and a caudal block with ropivacaine 2 mg ml^{-1}, 1 ml kg^{-1}, was performed. Ropivacaine was injected in fractions over ≤ 2 min. During anaesthesia, patients were monitored by ECG, pulse oximetry, capnography and non-invasive measurements of arterial pressure and inhalational agents. Opioids were avoided before or during surgery. However, according to our routine practice, all patients received paracetamol (total daily dose ≤ 100 mg kg^{-1}).

Blood and urine sampling

Peripheral venous blood samples (1 ml) for analysis of total plasma ropivacaine concentrations were collected from indwelling intravenous catheters immediately before and 15, 30, 60 min and 2, 4, 8 and 12–36 h after administration of caudal ropivacaine. Free ropivacaine and α_1-acid glycoprotein (AAG) concentrations were determined in the 30 min and 8 h samples, when larger volumes of blood (5 ml) were collected. The blood samples were centrifuged within 60 min of collection and the plasma was frozen at –20°C until assay.

In patients requiring urinary catheterization as a routine part of the surgical procedure, urine was collected for the determination of ropivacaine and its main metabolites, 3-hydroxyropivacaine and 2′,6′-pipecoloxylidide (PPX). Urine was collected every 6 h for ≤ 36 h postoperatively or until the urinary catheter was removed. The volume of urine collected at each occasion was recorded and 5 ml samples were frozen at –20°C until assay.

Bioanalytical methods

The total concentration of ropivacaine base (relative molecular mass 274) in plasma was determined by a gas-chromatographic method with nitrogen-sensitive detection.[6] The limit of quantification was optimized to 0.003 mg $litre^{-1}$ using 100 µl of plasma. The between-day coefficients of variation (CV) were <10% at concentrations in the range 0.0055–2.19 mg $litre^{-1}$. The accuracy was 99–101%. The free concentration of ropivacaine base in plasma was determined using a coupled-column, liquid-chromatographic system with UV detection after ultrafiltration of plasma at pH 7.4 and 37°C.[7] The limit of quantification was 0.003 mg $litre^{-1}$ using 1.0 ml of plasma. The between-day CV was 8.2% at a free ropivacaine concentration of 0.055 mg $litre^{-1}$. The concentration of AAG in plasma was determined by an immunoturbidometric method from Boehringer Mannheim. The limit of quantification was 0.12 g $litre^{-1}$ using 50 µl of plasma. The method was linear up to 5.33 g $litre^{-1}$. The between-day CV was 7% at 0.8 g $litre^{-1}$.

A new method was introduced for quantifying ropivacaine, 3-hydroxyropivacaine and PPX in urine. In previous studies, the concentration of ropivacaine and its main metabolites has been determined by a method based on liquid chromatography and UV detection.[8] In the present study, some patients were treated with trimethoprim, which was co-determined with 3-hydroxyropivacaine using unselective UV detection. A new method based on a selective detection technique, tandem mass spectrometry, was used in the present study. As before, the concentrations of ropivacaine, 3-hydroxyropivacaine (relative molecular mass 290) and PPX (relative molecular mass 232) in urine were determined after acid hydrolysis with 6 M hydrochloric acid. This gives the sum of the conjugated and the unconjugated 3-hydroxyropivacaine, while ropivacaine and PPX exist only in the unconjugated form. A urine volume of 1.0 ml was used. Solid-phase extraction was used for sample preparation. The new selective liquid-chromatographic method with gradient elution and electrospray tandem mass spectrometry was used for the determination of ropivacaine, 3-hydroxyropivacaine and PPX in urine. The gradient system contained acetonitrile and ammonium formate buffer, pH 4. The scan mode was multiple reaction monitoring using the precursor ions at m/z, M+1, 275.2 for ropivacaine, 291.1 for 3-hydroxyropivacaine and 233.2 for PPX. After collisional dissociation the product ions were used for quantification, m/z, 126.0 for ropivacaine and 3-hydroxyropivacaine and 84.0 for PPX. The limit of quantification was 0.08 mg $litre^{-1}$ for ropivacaine, 0.49 mg $litre^{-1}$ for 3-hydroxyropivacaine and 0.18 mg $litre^{-1}$ for PPX. The between-day CVs were <5% at ropivacaine concentrations of 0.15–4.6 mg $litre^{-1}$. For 3-hydroxyropivacaine, the between-day CVs were <8% at concentrations of 0.99–30 mg $litre^{-1}$ and for PPX they were <6% at concentrations of 0.42–11 mg $litre^{-1}$. The accuracy was 97–101%.

Pharmacokinetic calculations

The plasma concentration–time data were analysed by non-compartmental methods using the pharmacokinetic program WinNonlin Professional version 2.0 (Pharsight Co., Mountain View, CA, USA). Peak plasma concentration (C_{max}) and the time to C_{max} (t_{max}) were obtained directly from the observed data. The free fraction of ropivacaine (f_u) in a sample was calculated as free concentration divided by total concentration and the free ropivacaine concentration at t_{max} ($C_{u\ max}$) was estimated from C_{max} and $f_{u\ 30\ min}$, assuming the protein binding to be equal at 30 min and at t_{max}. The terminal half-life ($t_{1/2}$) was calculated by linear regression of the data points in the declining and linear part of the log-linear plasma concentration–time curve. The area under the plasma concentration–time profile up to infinity (AUC) was calculated using the linear trapezoidal rule up to the last blood sample and extrapolated to infinity by multiplying the concentration in the last measurable plasma concentration by $t_{\frac{1}{2}}$/ln2. The volume of distribution at steady state (V_{ss}) was calculated as dose × (AUMC)/AUC^2, where AUMC is the area under the first moment–time curve. Plasma clearance (*Cl*) was calculated as dose/AUC. Since the absorption of ropivacaine can be assumed to be complete after caudal administration, V_{ss} and *Cl* are not been presented as apparent parameters. *Cl* for the unbound concentration (Cl_u) was calculated as $Cl/f_{u\ 30\ min}$ and volume of distribution at steady state for the unbound fraction ($V_{ss\ u}$) was calculated as $V_{ss}/f_{u\ 30\ min}$. The hepatic extraction ratio (E_H) of ropivacaine was calculated as blood clearance divided by the liver blood flow (Q_H). The blood:plasma concentration ratio of ropivacaine was assumed to be similar to adult values (0.7), since the plasma protein binding of ropivacaine and the haematocrit have reached adult values in the age group studied.[9,10] Q_H was estimated from the adult value of liver blood flow, 1350 ml min^{-1}, adjusted to the individual body-surface area calculated as (weight (kg)/70 kg)$^{0.7}$×1.8.[11] The half-lives of 3-hydroxyropivacaine and PPX were estimated by linear regression of the linear and declining part of the log-linear plot of the excretion rate–time curve.

Clinical assessments

Postoperative analgesia and lower-limb motor function were assessed by the research staff at regular intervals, every hour during the first 8 h and then once within the interval 12–36 h. Postoperative pain was assessed using a four-point behaviour observer scale (no pain, mild pain, moderate pain, severe pain).[12] Supplemental opioid analgesia was administered if the pain was judged to be moderate or severe or the effect was considered insufficient by the research staff. The time to the first administration of opioid was recorded. Motor function was assessed as motor block present (inability to move the legs with slight stimulation allowed) or absent. Adverse events were recorded during the study period up to a telephone follow-up 2 weeks after surgery.

Statistical methods

The data were analysed using descriptive methods such as summary statistics and graphs. Possible relationships between variables were investigated using parametric linear regression. The results are presented as mean (SD) unless otherwise stated.

Results

Patient characteristics are shown in Table 1. There were five patients in the youngest age group, nine in the middle one and six in the oldest one. The main surgical diagnoses were hypospadia (*n*=7), undescended testis (*n*=6) and vesicoureteral reflux (*n*=2). The duration of surgery varied from 0.3 to 3.6 h. Two cases of protocol deviations (of minor importance) occurred: in one patient morphine 0.07 mg kg^{-1} i.v. was given as premedication and in another fentanyl 2×25 µg i.v. was given in connection with surgery.

Table 1 Summary of patient characteristics (median (range) or frequency)

n	**20**
Age (yr)	4.0 (1.3–7.6)
Weight (kg)	16.5 (11–25)
ASAI/ASAII	19/1
Gender (male/female)	18/2

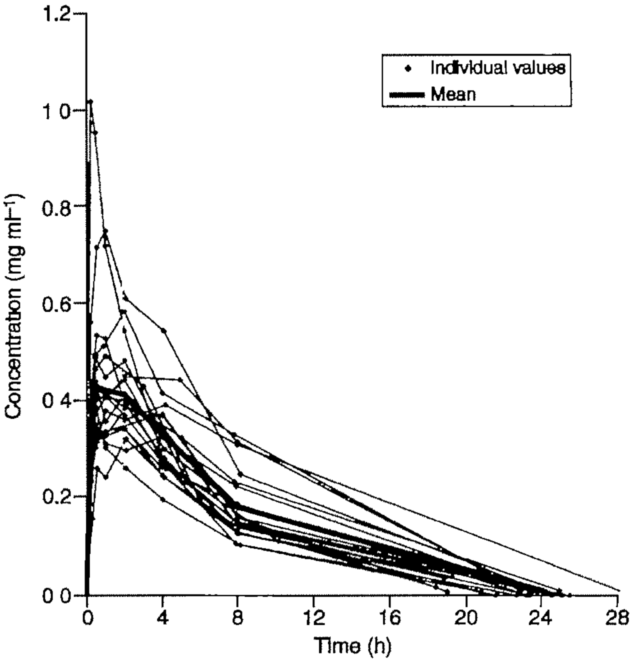

Fig 1 Individual and mean plasma concentration–time profiles of ropivacaine after caudal administration of ropivacaine 2 mg kg^{-1} to 1–8 yr old children (*n*=20).

Pharmacokinetics

The individual and mean plasma concentration–time curves are shown in Fig. 1. The pharmacokinetic parameters are reported for each age group and the entire population in Table 2. C_{max} and the estimated free plasma concentration of ropivacaine at t_{max} ($C_{u\ max}$) were similar in the age groups studied, whereas t_{max}, reached within 12 min to 4 h, tended to be shorter in older children. The highest individual C_{max}, 1.02 mg litre^{-1}, was observed 12 min after caudal block in a 2 yr old boy and the highest individual $C_{u\ max}$ was 0.043 mg litre^{-1} in a 3-yr-old girl. f_u was similar at 30 min and 8 h after the caudal block and in the three age groups. AAG concentrations at 30 min and 8 h were 10–22 and 11–24 µmol litre^{-1}, respectively. Half-life was in the range 2.3–5.5 h, with similar values in the three age groups. There was no apparent age-dependency in bodyweight-adjusted *Cl*

Table 2 Pharmacokinetics of ropivacaine after caudal administration at 2 mg kg^{-1} to 1–8 yr old children. The results are presented as mean (SD) (range) for all parameters, except t_{max}, which is expressed as median (range). [a]Estimated from C_{max} and $f_{u\ 30\ min}$ [b]n=3. [c]n=2.

	1–2 yr (n=5)	**3–4 yr (n=9)**	**5–8 yr (n=6)**	**Total (n=20)**
C_{max} (mg litre^{-1})	0 52 (0.28) (0.34–1.02)	0 47 (0.13) (0.32–0.75)	0 42 (0 07) (0 35–0 53)	0.47 (0.16) (0.32–1.02)
t_{max} (min)	115 (12–249)	62 (16–125)	30 (29–242)	60 (12–249)
$C_{u\ max}$ (mg litre^{-1})[a]	0.026 (0.013)[b] (0.014–0.039)	0 024 (0 008) (0 015–0 043)	0.023 (0.005) (0.014–0.029)	0.024 (0.008) (0 014–0 043)
f_u (%)				
30 min	4.7 (2.2) (3.0–7 3)[b]	5.2 (1.1) (3.0–7.1)	5.5 (1 3) (3.3–7.1)	5.2 (1.3) (3.0–7.3)
8 h	4.3 (1.3) (3.3–5.2)[c]	4.9 (1 5) (2.9–7 8)	5.4 (2.9) (3.3–10.9)	5.0 (2.0) (2.9–10 9)
Cl (ml min^{-1} kg^{-1})	6.4 (1.6) (4.6–8.0)	7.1 (1.6) (4.6–10 0)	8 8 (2 0) (5 9–11 8)	7 4 (1.9) (4 6–11 8)
Cl_u (ml min^{-1} kg^{-1})	146 (33) (109–167)[b]	140 (34) (78–189)	170 (67) (105–292)	151 (46) (78–292)
E_H (%)	0.29 (0 08) (0.21–0.37)	0.34 (0.08) (0.21–0 40)	0 45 (0 10) (0.30–0.57)	0 33 (0 12) (0 21–0.57)
V_{ss} (litres kg^{-1})	2 0 (0.4) (1.7–2 6)	2 5 (0.9) (1.4–4.3)	2 6 (0.5) (2.1–3 4)	2.4 (0.7) (1.4–4.3)
$V_{ss\ u}$ (litres kg^{-1})	46 5 (11 4) (35 2–58 0)[b]	48.8 (18.4) (23 3–90.0)	49 7 (15 1) (37 2–77 4)	45 5 (17 2) (23 3–90 0)
$t_{1/2}$ (h)	3.1 (0.8) (2.4–4.1)	3 4 (1.0) (2.3–5 5)	2 9 (0 5) (2 4–3.7)	3 2 (0 8) (2 3–5.5)

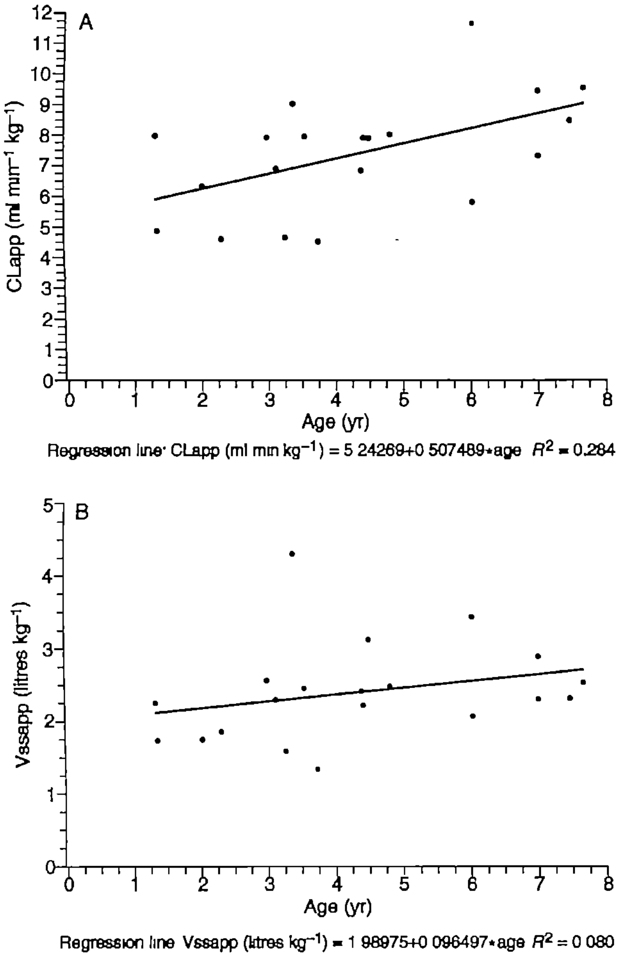

Fig 2 (A) Clearance/weight versus age and (B) V_{ss}/weight versus age after caudal administration of ropivacaine 2 mg kg^{-1} to 20 children aged 1–8 yr

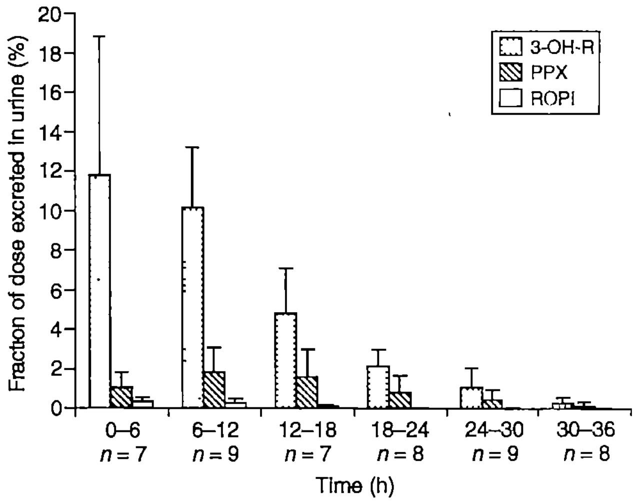

Fig 3 Mean (SD) fraction of dose excreted in urine as ropivacaine (ROPI) and its metabolites 3-hydroxyropivacaine (3-OH-R) and PPX after caudal administration of ropivacaine 2 mg kg^{-1} to 10 children aged 1–8 yr

(Fig. 2A) or in bodyweight-adjusted V_{ss} (Fig. 2B). The hepatic extraction ratio was low to intermediate. The results of the urinary excretion of ropivacaine, 3-hydroxyropivacaine and PPX are shown in Fig. 3. The mean total fraction of dose recovered in the urine as ropivacaine, 3-hydroxyropivacaine and PPX was 30%, with individual values between 12% and 48%. 3-Hydroxyropivacaine dominated with a mean recovery of 25%, range 10–44%. Between 1% and 12% of the dose was excreted as PPX (mean 5%), while no more than 1% of the dose was recovered in the urine as ropivacaine. In all infants the greatest amount of 3-hydroxyropivacaine was excreted within 0–12 h after the dose, whereas the greatest amount of PPX was excreted between 6 and 18 h. The half-life of 3-hydroxyropivacaine was in the range 4.0–6.3 h calculated on three to five data points (n=7); the half-life of PPX was 4.2–15.7 h as determined on the last two to four data points in six individuals.

Clinical assessments

The median time to supplemental analgesics (morphine) was 12.6 h after the block (Fig. 4). With the analgesic regime used, postoperative pain relief was satisfactory (i.e. no pain, mild pain or patient asleep) in ≥90% of the patients

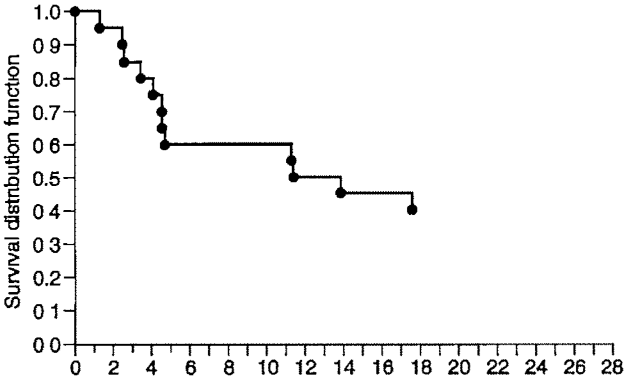

Fig 4 Time (in hours) from administration of ropivacaine to first dose of supplementary analgesics (other than paracetamol, which was given to all patients).

at all assessment times. No signs of motor block were observed in any of the patients during the postoperative period, and all children were able to move their legs when emerging from the anaesthesia. The most common adverse events were vomiting (50% of patients), nausea (15%) and pruritus (15%). No serious adverse reactions occurred and no signs or symptoms of other systemic toxic reactions were reported. Vital signs (arterial pressure, pulse rate and peripheral oxygen saturation) were measured and showed only minor variations from baseline.

Discussion

The major finding of the present study was that caudal block with ropivacaine 2 mg kg^{-1} (2 mg ml^{-1}) in children aged 1–8 yr results in plasma concentrations of unbound ropivacaine well below toxic concentrations in adults. The dose studied was associated with adequate postoperative analgesia and no signs of motor block or serious adverse reactions related to the use of ropivacaine were noted.

Since the registration of ropivacaine for use in adults, a limited number of clinical studies have been published regarding the use of this new local anaesthetic in children.[3–5] Caudal or epidural administration of ropivacaine 2 mg kg^{-1} has been reported to be comparable to bupivacaine 2.0–2.5 mg kg^{-1}.[3] Analgesia is significantly longer when using ropivacaine 5 mg ml^{-1} (3.75 mg kg^{-1}) than with either ropivacaine or bupivacaine 2.5 mg ml^{-1} (1.875 mg kg^{-1}).[13] Where 2.5–3.75 mg ml^{-1} solutions of bupivacaine and ropivacaine were used, ropivacaine administration was associated with a shorter duration of motor block.[14 15]

In the present study, the highest estimated individual peak plasma concentration of unbound ropivacaine was 0.043 mg litre^{-1} (mean 0.024 mg litre^{-1}) and the mean $C_{\max}$ of total ropivacaine was 0.47 mg litre^{-1}, which corresponds with previous data where single caudal doses of 1.875 mg kg^{-1} produced a $C_{\max}$ of *c.*0.6 mg litre^{-1} in 5 yr old children.[13] $t_{\max}$, which tended to be shorter in older children, was within the range normally observed in adults.[16] The acute tolerability of ropivacaine has been studied in healthy adult subjects. A threshold for central nervous system toxicity was apparent at mean (minimum–maximum) unbound arterial plasma concentrations of ropivacaine of the order of 0.6 (0.3–0.9) mg litre^{-1}.[1] Consequently, in the present study, the plasma concentrations of unbound ropivacaine were well below the threshold levels for toxicity in adults. AAG concentrations were similar 30 min and 8 h after caudal block and within ranges normally observed in healthy adult subjects[17] and in 1–5 yr old (ASA I–II) patients.[18] The free fraction of ropivacaine was in the range 3–11%, which is similar to the free fraction (6±1%) in adult patients 7–9 h after the start of an epidural infusion.[19] There was no apparent age-dependency in bodyweight-adjusted volume of distribution (mean 2.4 litres kg^{-1}). However, it was larger than the corresponding value in adults (0.7 litres kg^{-1}).[20]

Bodyweight-adjusted clearance was the same as in adults (5 ml min^{-1} kg^{-1})[20], without any apparent age-dependency. When estimating the hepatic extraction ratio in the present study, the hepatic blood flow was adjusted for body surface area, since hepatic blood flow in children correlates better with body surface area than with bodyweight.[11] The hepatic blood flows found in the present study correspond to values obtained by duplex Doppler ultrasound measurements in this age group.[21] Even if the estimation of the hepatic extraction ratio is based on assumptions, these are reasonable, and the extraction ratio value indicates that ropivacaine is handled as a drug with low to intermediate extraction characteristics by the liver, as in adults.[9] Consequently, ropivacaine clearance is expected to depend on the unbound fraction of ropivacaine rather than on the liver blood flow.

In the present study, the metabolic pattern of the main metabolites, 3-hydroxyropivacaine (25%) and PPX (5%), was similar to that found in adults, where 37% and 3% were excreted in the urine as 3-hydroxyropivacaine and PPX, respectively, with the remainder of the dose excreted as a number of quantitatively minor metabolites.[9] *In vitro*, cytochrome isoenzyme subclass CYP1A2 is responsible for the metabolism of ropivacaine to 3-hydroxyropivacaine and cytochrome isoenzyme subclass CYP3A4 is responsible for the metabolism of ropivacaine to PPX,[22] with CYP1A2 being the most important isozyme for the metabolism of ropivacaine *in vivo*.[23] The activity of CYP1A2 reaches adult levels in children above the age of 7 yr[24] and CYP3A4 reaches 30–40% of adult activity as early as 1 month after birth.[25] It is not surprising, therefore, that children above the age of 1 yr have a well developed capacity to eliminate ropivacaine.

Since neither the unbound volume of distribution nor the unbound clearance showed any apparent age-dependency when adjusted to bodyweight, dosing per kilogram of bodyweight is supported in this age group from a pharmacokinetic point of view.

There was no evidence of motor block in the lower limbs of any of the patients as they woke up. This finding is consistent with previous publications using ropivacaine 2 mg ml^{-1} in children.[3 4]

As a result of the variation in the dermatomal level of the surgical intervention and the duration of the surgical procedure, it is difficult to assess postoperative analgesia adequately. Although analgesia was not a primary end-point and a simple pain-scoring system was used, postoperative analgesia was assessed as satisfactory in ≥90% of the patients during the study period.

The most common adverse events (vomiting, nausea and pruritus) may have been associated with the surgical procedure, the general anaesthetic and postoperative opioid treatment and are commonly seen during the postoperative period.

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Pharmacokinetics of rectal paracetamol after repeated dosing in children

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Twenty-three children (aged between 9 weeks and 11 yr) were given paracetamol suppositories 25 mg kg^{-1} every 6 h (maximum 5 days) after major surgery and serum and saliva concentrations were measured. There was a good correlation (r=0.91, P<0.05) between saliva and serum concentrations. A one-compartment linear model with first-order elimination and absorption and lag-time was fitted to the data (ADAPT II). At steady state, the mean (SD) concentration was 15.2 (6.8) mg litre^{-1}. Mean (SD) time to reach 90% of the steady state concentration was 11.4 (8.6) h. Body weight, age and body surface area were well correlated (P<0.05) with clearance and apparent volume of distribution. There was no evidence of accumulation leading to supratherapeutic concentrations during this dosing schedule for a mean of approximately 2–3 days.

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Paracetamol has gained wide acceptance as a simple and safe antipyretic and analgesic in children. When oral administration is impractical, paracetamol is frequently given rectally. The administration of paracetamol to children is most commonly based on body weight.[1] Based on a computer simulation, it has been suggested that a rectal loading dose of 50 mg kg^{-1} followed by 30 mg kg^{-1} every 6 h should be the preferred regimen in children.[2] Several single dose studies have been carried out to investigate the pharmacokinetics of rectal paracetamol in children.[3–13] However, there is very limited clinical knowledge about the pharmacokinetics after repeated therapeutic doses in children,[14] partly as a result of blood sampling limitations and ethical considerations.

Paracetamol has been found to pass readily from blood to saliva via the salivary glands resulting in similar concentrations in adult volunteers[15] and patients.[16]

The purpose of this study was to confirm the correlation between serum and saliva concentrations and to investigate the pharmacokinetics of paracetamol after repeated rectal administration of 25 mg kg^{-1} every 6 h for 5 days in children.

Methods

Patients and protocol

Twenty-three children (ASA physical status I–II, aged between 9 weeks and 11 yr), scheduled for surgery with an anticipated need for analgesia for several days postoperatively were studied. The study protocol was approved by the regional Ethics Committee and the Danish Medicines Agency. Verbal and written information was given, and written informed consent was obtained from the parents. The children provided verbal assent to participate when possible and were excluded if they had received paracetamol 24 h prior to the time of surgery, had a history of liver disease, or paracetamol intolerance.

Anaesthesia was induced intravenously or with an inhalational agent and nitrous oxide/oxygen. Postoperatively, some children were given epidural bupivacaine/fentanyl and others had i.v. morphine either as patient controlled analgesia (PCA) or on a 'as required' basis. After induction of anaesthesia, the first dose of paracetamol 25 mg kg^{-1} was given. One or two of the five available suppository doses (50, 125, 250, 500, 1000 mg) were used to administer

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a dose as close as possible to 25 mg kg^{-1} for each child. Subsequent doses of paracetamol 25 mg kg^{-1} were given at approximately 6 hourly intervals for up to 5 days postoperatively.

Saliva and blood samples were obtained immediately before insertion of suppositories and at 1, 2, 3 and 4 h after the administration of the first dose. On the following days, blood and/or saliva samples were taken before administration of the morning dose and at 1, 2, 3 and 4 h after these morning doses. Paracetamol was administered for up to 5 days. Blood samples were drawn from a central venous catheter or a peripheral vein. Saliva samples were obtained using the Salivette citrus device (Sarstedt Laboratories, Nümbrecht, Germany) developed especially for saliva sampling. The Salivette citrus consists of a cotton wool swab (containing 25 mg citric acid to stimulate saliva production), which is placed in the oral cavity for 2–3 min.[17] A string was attached to the swab to avoid accidental swallowing. Binding of paracetamol to the swab was investigated prior to this study and was found to be a maximum of 2% when compared with saliva samples collected by spitting. Citric acid did not interfere with the analysis and stimulation of saliva production and had no influence on the concentration of paracetamol in saliva.[18] The exact dose and time of administration was noted along with the time of collection of blood and saliva samples.

Analysis of samples

Saliva samples were kept refrigerated at 4°C for a maximum 1 h until the saliva was centrifuged out of the swab. Blood samples were allowed to clot for 1 h before serum was separated by centrifugation. Immediately after centrifugation, saliva and serum samples were frozen at –20°C until assayed. Saliva and serum samples were stable at –20°C for at least 6 months. After thawing, 60 μl of sample was mixed with 120 μl of a protein precipitating solution (2% $ZnSO_4.7H_2O$ in 1:1 methanol/water) containing the internal standard (metacetamol, 6 mg $litre^{-1}$) and whirl-mixed for 30 s before centrifugation at 10 000 *g* for 10 min.

Paracetamol concentration was determined by high performance liquid chromatography (HPLC). The HPLC system consisted of a Merck Hitachi automatic integrated system with a L-7100 pump, L-7400 UV-detector, L-7200 autosampler and a D-7500 integrator. A Spherisorb RP-18 (250×4.6 mm, 5 μm) column and a LiChrospher 100 RP-18 (5 μm) pre-column were used. The chromatographic conditions were as follows: wavelength 248 nm, mobile phase flow 1 ml min^{-1}, the mobile phase consisted of acetonitrile–0.1 M sodium acetate pH=4 (20:80 v/v). Triethylamine 150 μl was added per litre of mobile phase. The injection volume was 20 μl. Standard curves were linear in the range 0–40 mg $litre^{-1}$. The intra day coefficient of variation was 6.7% at 0.05 mg $litre^{-1}$ and 0.4% at 40 mg $litre^{-1}$. The between-day coefficient of variation was 0.8–2.2% when concentrations ranged from 1–40 mg $litre^{-1}$.

Statistics and pharmacokinetic modelling

Data are presented as mean values with SD, median and ranges as appropriate. Pearson's correlation was used for analysis of saliva–serum correlations and to evaluate the influence of demographic data on pharmacokinetic parameters. Statistical significance was defined as $P<0.05$.

Pharmacokinetic modelling was performed using the computer program ADAPT II, release three (D.Z. D'argenio and A. Schumitzky, University of Southern California, USA, 1992).

A one-compartment linear model with first-order elimination and absorption and lag-time was fitted to the data. The goodness of fit was evaluated by visual inspection of predicted *vs* observed data and from plots of residuals.

The absorption rate constant (k_a), lag-time (t_{lag}), elimination rate constant (k_e), elimination half-life ($t_{\frac{1}{2}}$), apparent volume of distribution (V_d/F, F=absorption fraction), and apparent clearance (CL/F) were estimated by the ADAPT II program for each patient. The maximum concentration $C_{max(1)}$ and the time to reach the $C_{max(1)}$ $T_{max(1)}$ in the first dosing interval was calculated by $C_{max(1)}=[(D \cdot F/V_d)(k_a/k_e)^{(ke/(ke-ka))}]$ and $T_{max(1)}=[(1/(k_a-k_e))(\ln(k_a/k_e))]$ respectively [19], where D represents the dose.

The average concentration at steady state (C_{ss}) was calculated for each patient by using the van Rossum's equation[20] $C_{ss}=[(D/\tau)/(CL/F)]$, where τ is the dosing interval. The median of τ for each patient was used for this purpose.

In each case the time to reach 90% of the steady state concentration ($T_{Css\ (90\%)}$) was calculated using the equation [21] $T_{Css\ (90\%)}=3.3 \cdot t_{\frac{1}{2}}$.

Simulation of the recommended dosing schedule was done in Quattro Pro 6.0 using the equation,

$$C(t) = \frac{FD}{V_d} * \frac{k_a}{k_a - k_e} * \left[\frac{(1 - e^{-nk_e\tau})}{(1 - e^{k_e\tau})} * -e^{-k_e(t-t_{lag})} - \frac{(1 - e^{-nk_a\tau})}{(1 - e^{-k_a\tau})} * e^{-k_a(t-t_{lag})} \right]$$

where n represents the number of doses given.[19]

Results

Twenty-three children were included in the study. Two were excluded because of mishandling of saliva and serum samples. Patient characteristics of the remaining 21 children, individual doses and length of paracetamol treatment (LOT), which was determined as the time from first to last paracetamol dose according to the protocol was administered, are shown in Table 1.

No paracetamol was detected in the serum or saliva samples taken before administration of the first study dose.

Table 1 Patient and clinical data for all patients. BMI=body mass index[22] calculated as [(body weight in kilograms)/(height in metres)^2], BSA (in m^2)=body surface area[23] calculated as [(body weight in kilograms)$^{0.425}$ (height in centimetres)$^{0.725}$×71.84×10^{-4}], LOT=length of treatment, determined as the time from first to last administration of paracetamol suppositories *Patients are not included in calculation of mean (SD), median, or range. **Only one dose was given (see text for details)

Patient	Age (yr)	Sex (M/F)	Weight (kg)	Height (cm)	BMI (kg m^{-2})	BSA (m^2)	Dose (mg kg^{-1})	No. of doses (*n*)	LOT (h)	No. of saliva and blood samples (*n*)
1	7.0	F	20.0	120.0	13.9	0.83	25.0	5	21.8	12
2	7.0	M	28.0	129.0	16.8	1.00	26.8	5	19.5	5
3	8.0	M	23.0	115.0	17.4	0.85	23.9	9	43.8	23
4	3.0	M	16.0	98.0	16.7	0.65	23.4	13	65.8	15
5	9.0	F	24.0	–	–	–	26.0	16	94.8	14
6	4.0	M	17.0	110.0	14.0	0.72	22.1	12	69.98	19
7	6.0	M	24.0	122.0	16.1	0.91	22.9	17	92.8	24
8*	7.0	M	20.0	120.0	13.9	0.83	25.0	1	0**	5
9	9.0	M	37.0	150.0	16.4	1.26	27.0	8	40.4	13
10	10.0	M	25.0	128.0	15.3	0.95	25.0	6	46.6	10
11*	6.5	M	23.5	125.0	15.0	0.91	23.4	1	0**	3
12*	3.0	M	18.0	102.0	17.3	0.71	27.8	1	0**	4
13	0.2	M	6.0	63.0	15.1	0.31	20.8	13	63.4	13
14	11.0	F	38.0	155.0	15.8	1.32	26.3	12	71.8	24
15*	5.0	F	21.5	114.0	16.5	0.81	25.6	1	0**	3
16	0.2	F	5.6	59.0	16.1	0.29	22.3	17	95.6	19
17	5.0	M	19.0	109.0	16.0	0.76	26.3	16	93.3	21
18	0.2	M	5.5	61.0	14.8	0.30	22.7	12	67.6	13
19	0.2	M	5.2	59.0	14.9	0.28	24.0	16	91.3	19
20	7.0	M	32.0	139.0	16.6	1.12	23.4	9	44.3	13
21	3.0	M	15.1	100.0	15.1	0.65	24.8	9	48.9	13
Mean	5.3		20.0	107.8	15.7	0.76	24.3	11.5	63.0	15.9
SD	3.6		10.2	31.0	1.0	0.33	1.8	4.0	24.4	5.2
Median	6.0		20.0	112.5	15.9	0.80	24.0	12.0	65.8	14.0
Range	0.2–11.0	16/5	5.2–38.0	59.0–155.0	13.9–17.4	0.28–1.32	20.8–27.0	5–17	19.5–95.6	5–24

Saliva–serum correlation

Thirty-two paired samples (n=64) were available for correlation analysis. The samples were obtained from 12 different children aged between 11 weeks and 11 yr. The data are depicted in Figure 1A. Regression analysis resulted in a Pearson's Correlation coefficient (r) of 0.91 (P<0.001). The constant of the regression line was not significantly different from zero (P=0.6) and the data were then fitted to the simpler model forcing through the origin. The relationship between serum and saliva concentrations could be described by the following equation (mg litre^{-1}):

$$\text{concentration}_{\text{saliva}}=0.92\times\text{concentration}_{\text{serum}}$$

The ratio between saliva and serum was calculated to be 0.92±0.26 (Fig. 1B).

Pharmacokinetic modelling

Data from 17 children were used in the following modelling as four children (8, 11, 12 and 15 in Table 1) were excluded because of insufficient data.

Individual parameters of k_a, t_{lag}, k_e, $t_{\frac{1}{2}}$, V_d/F, CL/F, C_{ss} and $T_{Css(90\%)}$ are given in Table 2.

In Figure 2A a serum concentration–time profile for a typical patient is shown. One patient (14) among the 17 patients subjected to pharmacokinetic modelling was excluded from average estimates in Table 2 because this patient exhibited very different parameter values and did not

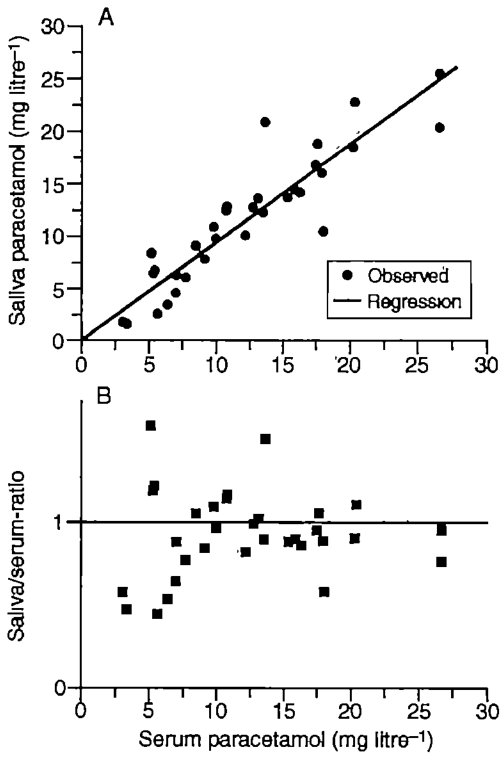

Fig 1 (A) Plot of saliva *vs* serum concentrations. The line indicates the line of regression. concentration$_{\text{saliva}}$=0.92×concentration$_{\text{serum}}$. (B) Ratio between saliva and serum concentrations. The mean ratio was 0.92 (SD 0.26). The line indicates the line of unity.

Table 2 Pharmacokinetic data. k_a=absorption rate constant; t_{lag}=lag time; k_e=elimination rate constant; $t_{\frac{1}{2}}$=elimination half-life; V_d/F=apparent volume of distribution; $C_{max(1)}$=maximum concentration in the first dosing interval; $T_{max(1)}$=time to reach $C_{max(1)}$, CL/F= apparent clearance, F=absorption fraction, τ=dosing interval, C_{ss}=average concentration in steady state, $T_{Css\ (90\%)}$=time to reach 90% of C_{ss}. *Patient is not included in the calculation of mean, SD, median, or range (see text for details)

Patient	k_a (h^{-1})	t_{lag} (h)	k_e (h^{-1})	$t_{1/2}$ (h)	V_d/F (litre kg^{-1})	$T_{max(1)}$ (h)	$C_{max(1)}$ (mg $litre^{-1}$)	CL/F (litre kg^{-1} h^{-1})	τ (h)	C_{ss} (mg $litre^{-1}$)	$T_{Css\ (90\%)}$ (h)
1	0.95	0 29	0.12	6.00	2.65	2.49	6.99	0 31	5 00	16 32	19.79
2	3.96	0.87	0 06	11 46	2 74	1.07	9 17	0 17	4.38	36 91	37 81
3	0.28	0 00	0 28	2.45	0.75	3.53	11.75	0.21	5 35	21.01	8 09
4	0 19	0 25	0 19	3 64	1.04	5.26	8.28	0.20	6.00	19.84	12 02
5	9.29	0.98	0 19	3 57	1 26	0.43	19.05	0.24	6.00	17.77	11 78
6	0.52	0.00	0.12	5.98	2.02	3 67	7.03	0.23	6 00	15.66	19 72
7	0 55	0 76	0 55	1.26	0 50	1 81	16 87	0 28	6 00	13 84	4 14
8	–	–	–	–	–	–	–	–	–	–	–
9	0.54	0.68	0 54	1.27	0.83	1.84	11.99	0.45	6 00	9 99	4 20
10	0.30	0.41	0 29	2.35	1.07	3 39	8.74	0 31	8 50	9 37	7 76
11	–	–	–	–	–	–	–	–	–	–	–
12	–	–	–	–	–	–	–	–	–	–	–
13	0.36	0.77	0.36	1.92	0 86	2 77	8.92	0 31	5.00	13.39	6.34
14*	1.61	0.00	0.03	20.82	9.46	2.52	2 58	0.28	6.00	13 92	76 25
15	–	–	–	–	–	–	–	–	–	–	–
16	0.65	1.55	0.65	1.07	0 86	1.54	9 57	0.56	6 00	6 69	3.52
17	0 40	0.33	0.33	2.10	1.11	2.75	9.57	0.37	6.00	11.96	6.94
18	0 53	0.05	0.53	1.32	0 78	1.90	10.73	0.41	6 00	9.19	4 35
19	0.84	0.00	0.30	2.29	1.05	1.91	12 92	0.32	5 84	12 97	7 56
20	1.52	0 72	0 14	5 12	1.96	1.73	9.39	0.27	5 50	16 06	16 89
21	1 17	0 59	0.21	3.36	1.64	1.79	10.40	0 34	6 00	12.22	11 08
Mean	1.38	0 52	0 30	3.45	1.32	2.37	10.71	0.31	5 85	15.20	11.38
SD	2.22	0.42	0 17	2 59	0 66	1 10	3 09	0 10	0 84	6.78	8 55
Median	0 55	0.50	0.29	2.40	1.06	1.91	9.57	0 31	6 00	13.61	7 93
Range	0.19–9.29	0–1.60	0.06–0 65	1 07–11 46	0.50–2.74	0 43–5 26	6.99–19 05	0 17–0 56	4.38–8 50	6 69–39 91	3 52–37 81

reach steady state within the 75 h of sampling. The serum concentration–time profile for this patient is shown in Figure 2B.

The Pearson's Correlation coefficients (r) between the apparent volume of distribution (V_d/F) and age, height, body weight, and body surface area (BSA)[23] were found to be 0.57, 0.70, 0.67 and 0.69 respectively. The Pearson's Correlation coefficients (r) for the relationship between the apparent clearance (CL/F) and the patient characteristics mentioned above were 0.74, 0.79, 0.83 and 0.82. All correlations were statistically significant (P<0.05) and are depicted in Figure 3A–D. There was no correlation between body mass index (BMI)[22] and V_d/F or CL/F. Patients 8, 11, 12, 14 and 15 were excluded from calculations of Pearson's correlation coefficients.

Concomitant administration of drugs was registered for all patients (Table 3). There are no reports on interactions between paracetamol and any of these drugs[24] and regional anaesthetic techniques are not known to affect paracetamol pharmacokinetics.

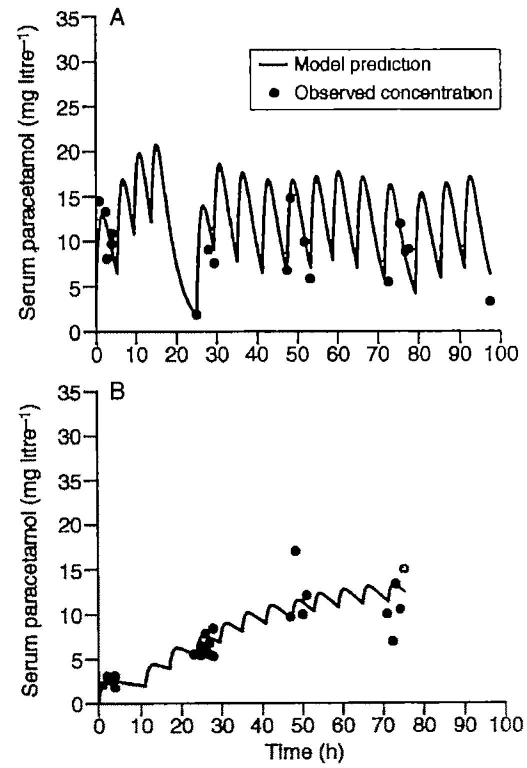

Fig 2 Observed *vs* predicted serum concentration time-profiles of paracetamol. (A) A typical patient (no. 19). (B) An atypical patient (no 14).

Discussion

Saliva sampling represents a non-invasive method, which is not associated with pain and the risk of infection present in blood sampling. It is especially advantageous when multiple samples are required. The good correlation between saliva

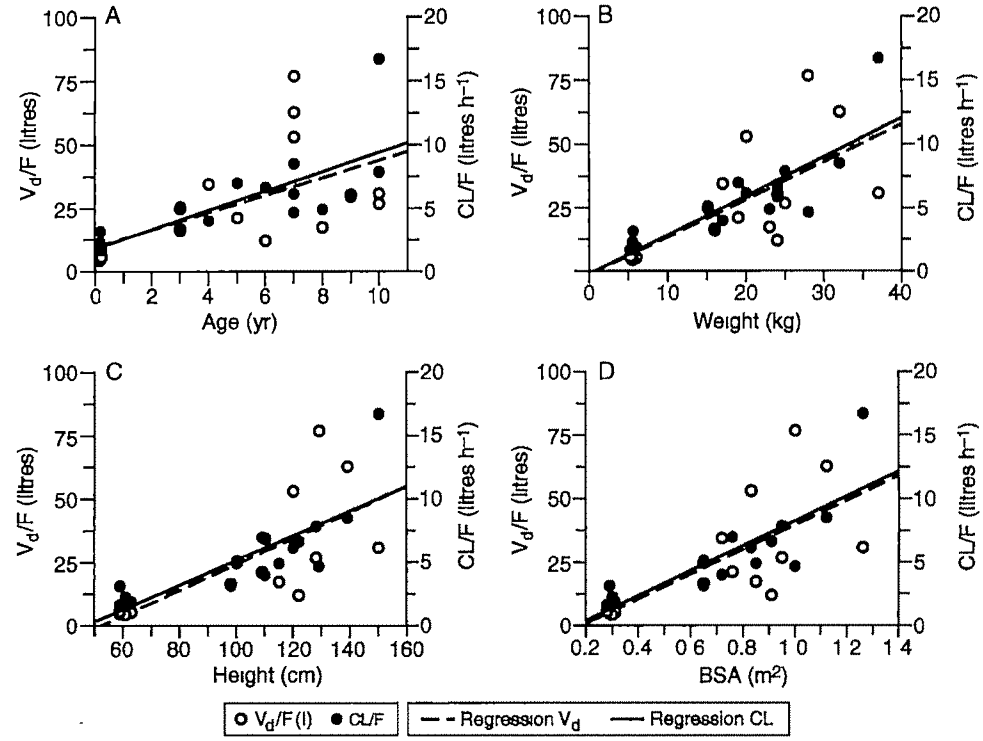

Fig 3 Volume of distribution (V_d/F) and clearance (CL/F) compared to age, weight, height and BSA. The lines indicate lines of regression Correlation coefficients (r) between V_d/F and weight, height, and BSA were 0.57, 0.70, 0.67 and 0.69, respectively, and between CL/F and the parameters mentioned above correlation coefficients were 0.74, 0.79, 0.83 and 0.82. All correlations were statistically significant ($P<0.05$)

Table 3 Concomitant drug administration during study period Numbers refer to patient numbers in Tables 1 and 2

Concomitant drug	Patients exposed
Diclofenac	1, 2, 3, 5, 7, 9, 11, 17
Morphine	5, 9, 11, 17, 19, 20, 21
Epidural bupivacaine	4, 6, 10, 21
Fentanyl	4, 5, 21
Alfentanil	6
Pethidine	5
Benzylpenicillin	1, 2, 3, 7, 9, 11, 17
Cefuroxime	5
Dexamethasone	1, 2, 7, 9, 11, 17
Ondansetrone	9, 17, 21
Furosemide	14

and serum concentrations of paracetamol found in the children in our study is in agreement with findings in another study of adult postoperative patients,[16] where the correlation coefficient (r) after rectal administration of paracetamol was 0.99 compared with 0.91 in our study. Al-Obaidy and colleagues[25] found a correlation coefficient (r) of 0.95 after oral dosing in six paediatric patients. This suggests that saliva samples can replace blood samples in assessment of paracetamol concentrations in children in the postoperative period. Saliva sampling has been observed to result in cost savings compared to blood sampling and to be more acceptable to parents and children.[26]

After administration of paracetamol suppositories, the absorption rate was faster than or equal to the rate of elimination in all children, but large variations were seen in the absorption phase and the resulting steady state concentrations. The absorption rate constant (k_a) observed in our study was 1.4 (2.2) h^{-1}. After administration of suppositories to children, Birmingham and colleagues[3] reported a typical k_a of 0.3 h^{-1} and Coulthard and colleagues[8] found a mean k_a of 1.4 h^{-1}.

Various explanations have been offered for this unpredictable absorption pattern from paracetamol suppositories, but none have been proven. Premature defaecation would reduce the amount of drug available for absorption, but no premature defaecation was observed in our study. Rectal pH and rectal contents may also influence the absorption pattern of rectally administered drugs [27]. In children, the rectal pH varies from 7.8–11.4 (95%-confidence interval).[28] For paracetamol (pKa=9.5) this may influence bioavailability, since only undissociated drug passes biological membranes and the degree of dissociation for paracetamol will vary from 2 to 99% in this pH range (% molar dissociation=[100/(1+antilog pKa–pH)]).[29]

Children seem to absorb paracetamol from suppositories faster and to a greater extent than adults. Using the same type of suppositories in a single dose of 26–36 mg kg^{-1} in adults after minor gynaecological laparoscopic surgery,[16] the highest mean (SD) observed concentration was 8.4 (3.5) mg $litre^{-1}$ compared with the C_{max} after the first dose in our study which was 10.7 (3.1) mg litre^{-1} after administration of 21–27 mg kg^{-1}. Giving 23.9 (4.2) mg kg^{-1} to children younger than 160 days, Hansen and colleagues[30] observed a C_{max} of 10.9 mg litre^{-1}. In a study of adults,[16] T_{max} was not reached within 4 h after administration. In contrast, T_{max} in the first dosing interval for the children in our study was 2.4 (1.1) h. Values of T_{max} found by other investigators after single dose administration of paracetamol suppositories to children are between approximately 1 and 3 h.[3 4 8 10 30–32] In pre-term neonates, the absorption seems to be slower, van Lingen and colleagues found T_{max} values of 3.9–5.1 h in children 28–36 weeks of gestational age.[33]

The limited space in the rectum of infants and small children compared with suppository size may favour a more efficient contact with the rectal mucosa and, consequently, improved absorption. Also, the rectal mucosa and colonic blood flow may be altered in children, but this has not been proven.

Differences in the concentration reached in individual patients may also be explained by a variability of venous drainage from the rectum. Paracetamol undergoes variable hepatic first-pass metabolism.[31 34] If a drug is administered in the upper part of rectum it will be subject to the hepatic first pass effect whereas drugs in the lower part of the rectum will bypass the liver via the inferior vena cava.[35] Administration of multiple suppositories, as was the case for some children in our study, could also contribute to the variable absorption.[36] The degree of rectal anastotomic channels has been proposed to counteract the rectal venous drainage pattern.[7]

The volume of distribution (V_d/F) in our study is in agreement with values found in other paediatric studies.[11 32 37] The lower correlation coefficient (r=0.57) between age and V_d/F implies that calculation of a loading dose should not be based on age but rather on weight, height or BSA, which show higher correlations to the apparent volume of distribution (r=0.67–0.70).

Only 4% of paracetamol is excreted unchanged in the urine in both neonates, children and adults. The rest is metabolized to paracetamol-sulphate and glucoronide in varying amounts depending on age.[38 39] Even though neonates, infants and children under 12 yr have a limited ability to conjugate phenolic drugs they are able to compensate for this by a well-developed capability for sulphate conjugation, resulting in overall paracetamol elimination half-lifes after single doses similar to adult values.[39 40] In our study $t_{\frac{1}{2}}$, after repeated dosing, was between 1.1 and 11.5 h with a mean (SD) of 3.5 (2.6) h, and for one patient (14) the $t_{\frac{1}{2}}$ was as long as 20.8 h, but the predicted steady state concentration for this patient was in the therapeutic range. The long $t_{\frac{1}{2}}$ may reflect a very slow rate of absorption, i.e. a flip-flop model, and not a reduced clearance, as the steady state concentration for this patient was comparable with the steady state concentration of the other patients. Repeated doses to children aged between 6 months and 6 yr in a study by Nahata and colleagues resulted in a $t_{\frac{1}{2}}$ of 2.2 h.[14]

The relatively good correlation (r=0.72, P<0.05) between CL/F and age suggests that the ability to eliminate paracetamol does increase slightly with age (Fig. 3A). However, body weight (Fig. 3B) and BSA (Fig. 3D) seem to correlate better with elimination capacity (r=0.83 and 0.82, P<0.05). In six pharmacokinetic studies of paracetamol including a total of 270 children between 2 months and 17 yr the terminal half-life after single doses ranged from 1.7 to 4.7 h.[4 8 11 30 32 37] In pre-term neonates the half-life seems to be prolonged. For example, van Lingen[33] observed a $t_{\frac{1}{2}}$ of 4.8–11.0 h in this age group.

The average concentration reached at steady state (C_{ss}) in our study (15.2 (6.8) mg litre^{-1}) is well above the lower limit for the accepted antipyretic concentration range, which has been suggested to be 10–20 mg litre^{-1}.[41–43] Only one patient did not approach this concentration range at steady state. Although no solid link has been proven to exist between serum concentration of paracetamol and degree of analgesia produced, the analgesic effect of paracetamol is believed to be related, directly, to its serum concentration[44] because of its high lipid solubility and low protein binding in the therapeutic concentration range. After tonsillectomy in children two studies have reported relationships between paracetamol concentration and degree of postoperative pain. Anderson and colleagues[2] observed that 50% of children experienced satisfactory analgesia at a concentration of 17 mg litre^{-1}, and in another study,[13] acceptable pain scores were associated with a paracetamol concentration above 10 mg litre^{-1}.

The safety of repeated dosing of paracetamol in children has been questioned,[14 33 45] and cases of toxicity after repeated therapeutic doses[46 47] and supratherapeutic doses[48] have been reported. In our study the highest predicted concentration at steady state was 36.9 mg litre^{-1} which is well below the limit of toxicity[49 50] at 120 mg litre^{-1}. However, care should be taken when situations of malnutrition are present, because depletion of glutathione stores could make children susceptible when sulphation and glucoronidation pathways are saturated.[51–53]

The maximum daily dose of paracetamol is controversial,[54] but the current oral paediatric dosing recommendation for paracetamol is a loading dose of 20 mg kg^{-1} and a maintenance dose of 15 mg kg^{-1} every 4 h[55] with an upper limit of 90 mg kg^{-1} per day.[56] Rectally 15–20 mg kg^{-1} is given every 4 h commonly,[57] but this may produce inadequate concentrations.[58 59]

To reduce the time to reach steady state concentrations, which in our study were not reached until nearly 12 h after administration of the first dose, a loading dose should be given.

We used mean parameter values found in this study (k_a=1.4 h^{-1}, t_{lag}=0.5 h, k_e=0.3 h^{-1}, V_d/F=1.3 litre kg^{-1}, CL/F=0.3 litre kg^{-1}h^{-1}) to simulate a paracetamol dosing schedule with a loading dose of 35 mg kg^{-1} and a

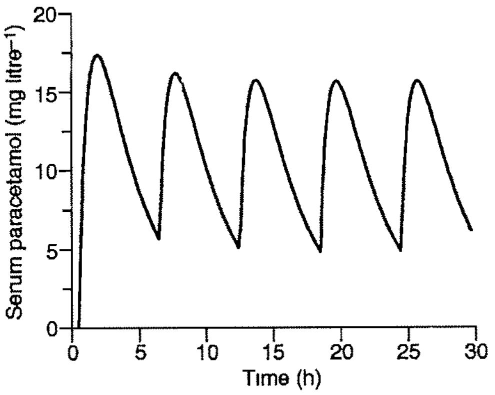

Fig 4 Simulation of serum concentration time-profile showing a dosing schedule with a loading dose of 35 and 25 mg kg^{-1} administered as suppcsitories every 6 h. Parameter values used were k_a=1.4 h^{-1}; t_{lag}=0.5 h; k_e=0.3 h^{-1}; V_d/F=1.3 litre kg^{-1}, CL/F=0.3 litre kg^{-1} h^{-1}. Simulation was done using the equation:

$$C(t) = \frac{FD}{V_d} * \frac{k_a}{k_a - k_e} * [\frac{(1 - e^{-nk_e\tau})}{(1 - e^{k_e\tau})} * -e^{-k_e(t-t_{lag})} - \frac{(1 - e^{-nk_a\tau})}{(1 - eSUP - k_a\tau)} * e^{-k_a(t-t_{lag})}]$$

where *n* represents the number of doses given.[19]

maintenance dose of 25 mg kg^{-1} administered as suppositories every 6 h (Fig. 4).

In conclusion, after administration of paracetamol suppositories to children blood samples can be replaced by saliva samples in the postoperative period, and a loading dose of 35 mg kg^{-1} followed by 25 mg kg^{-1} rectal paracetamol every 6 h for 2–3 days to children aged between 9 weeks and 11 yr produces steady state concentrations in the anticipated antipyretic and analgesic range with no sign of accumulation or adverse effects. This dosing schedule is recommended for otherwise healthy infants and children in the postoperative period. A more cautious dosing regimen should probably be followed in children who have been fasted for a longer period or with concomitant diseases.

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Peripheral lidocaine but not ketamine inhibits capsaicin-induced hyperalgesia in humans

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We examined the effect of the subcutaneous infiltration of ketamine, lidocaine and saline before injury on capsaicin-induced pain and hyperalgesia. Twelve healthy volunteers participated in two separate, randomized, double-blind, placebo-controlled crossover experiments. In experiment 1, 100 μg capsaicin was injected intradermally in one volar forearm 10 min after the skin had been pretreated with lidocaine 20.0 mg in 2.0 ml or 0.9% saline 2.0 ml at the capsaicin injection site. In experiment 2, a similar capsaicin test was given 10 min after the skin had been pretreated with ketamine 5 mg in 2.0 ml or 0.9% saline 2.0 ml. To control for possible systemic effects, the capsaicin injection site was pretreated by injection of saline into the skin and the contralateral arm was treated with active drug, and vice versa. Outcome measures were spontaneous pain, pain evoked by punctate and brush stimuli, and areas of brush-evoked and punctate-evoked hyperalgesia. Lidocaine reduced all measures compared with placebo ($P<0.001$), whereas ketamine failed to change any measures. Pain scores and areas of hyperalgesia were not affected when the contralateral site was infiltrated with ketamine or lidocaine. Lidocaine produced no side-effects, whereas ketamine produced paraesthesia, dizziness and sleepiness in six out of 24 (25%) cases. Blocking peripheral sodium channels with locally administered lidocaine reduces spontaneous pain and capsaicin-induced hyperalgesia but local block with the NMDA-type glutamate receptor antagonist ketamine has no effect on capsaicin-induced pain and hyperalgesia.

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Intradermally or topically applied capsaicin is a widely used model of experimental hyperexcitability in humans. Previous studies have shown that capsaicin-induced hyperexcitability involves peripheral and central hyperexcitability[1–6] and that this hyperexcitability is amenable to block with *N*-methyl-D-aspartate (NMDA)-type glutamate receptor antagonists and sodium channel blockers. Ketamine, a non-competitive NMDA receptor antagonist, reduces the excitatory responses of wide dynamic range neurones in the spinal cord and mechanical hyperalgesia in animals[7–9] and reduces spontaneous pain and hyperalgesia in experimental and clinical pain states in humans.[10–17] The modulating effects of systemic ketamine on pain and hyperalgesia were previously attributed to an action on the NMDA receptor system in the central nervous system[18 19] (the spinal cord or more centrally), but the recent anatomical demonstration of NMDA receptors in the peripheral nervous system has raised the possibility that the pain-relieving effect of ketamine is also mediated peripherally. For example, Carlton and colleagues[20] demonstrated glutamate receptors on peripheral unmyelinated axons in rats, and these authors also showed that activation of these receptors gave rise to mechanical hyperalgesia that could be inhibited by local treatment with NMDA receptor antagonists.[20–22]

Reports of the effects of locally administered ketamine on human experimental pain are not consistent. In a burn injury model, Warncke and colleagues[23] showed that local treatment with ketamine before injury inhibits the development of mechanical hyperalgesia. As the effect of ketamine was compared directly with that of saline in the same session, it

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is possible that the effect observed was systemic and not local alone. In a recent human study by Pedersen and colleagues,[24] peripheral ketamine treatment reduced spontaneous pain during the induction of burn injury and increased the threshold for heat pain. However, the number of side-effects reported was similar regardless of which side was treated with ketamine. Saline on both sides produced markedly fewer side-effects. Therefore, the observed effect of ketamine could be peripheral as well as systemic.

Pre-injury block with local anaesthetics may prevent or reduce central alterations after a peripheral injury.[25 26] Lidocaine is a use-dependent sodium channel blocker. Pre-injury infiltration with lidocaine has been shown to inhibit the development of mechanical hyperalgesia in the capsaicin model[3] and in a burn injury model[27] in humans, indicating that hyperalgesia can be blocked by a peripherally acting analgesic.

Therefore, this study examined the analgesic effect of local treatment before injury with the NMDA receptor antagonist ketamine, the sodium channel blocker lidocaine and saline on the pain and hyperalgesia induced by intradermally applied capsaicin. We used a study design that permitted control for a possible systemic effect of local ketamine and lidocaine.

Materials and methods

Subjects

Twelve healthy male volunteers participated in two separate experiments and 11 participated in both experiments. The primary effect parameters were the areas of brush-evoked and punctate-evoked hyperalgesia and the secondary effect parameters were spontaneous pain and evoked pain, scored on a visual analogue scale (VAS). The number of subjects needed to detect an effect on the area of hyperalgesia was calculated as 10 (SD 15) cm^2 (the expected reduction of 50% of a mean area of 36–40 cm^2; α=0.05, β=0.80). To detect an effect on VAS scores, a smaller number of subjects was needed. Each experiment was performed in a randomized, double-blind, placebo-controlled crossover design. Informed written consent was obtained from all participants before the start of the study, and the study was approved by the local Ethics Committee and by the Danish National Board of Health.

Intradermal capsaicin and drug administration

Capsaicin (8-methyl *N*-vanillyl 6-nonamide) (Sigma, St. Louis, MO, USA) was dissolved in Tween 80 by heating.[28] Saline was added under sterile conditions to obtain a concentration of 5 mg ml^{-1}. To familiarize the subjects with capsaicin pain and the tests performed during each trial, 50 µg of capsaicin was injected in the left volar forearm at least 1 week before the first trial. Subjects who failed to develop allodynia at the screening session were not included in the study. In each experiment, capsaicin was injected in the right forearm in half of the subjects and in the left forearm in the remaining subjects, in random order A person not involved in the testing prepared the randomization codes and the drugs used for injection, which were in identical syringes.

Experiment 1

On each of two examination days, separated by at least 1 week, subjects received pre-injury subcutaneous infiltration with lidocaine 20 mg in 2.0 ml (Lidokain. SAD, Copenhagen, Denmark, pH=5.5) or isotonic 0.9% saline in 2.0 ml (NaCl, SAD, pH=6.0) at the site where capsaicin was to be injected. The subcutaneous infiltration was done over an area of approximately 3 cm^2 around the capsaicin injection site. To examine for a possible systemic effect of the active drug, capsaicin was injected into saline-pretreated skin and the contralateral arm was injected with active drug, and in other tests capsaicin was injected into skin pretreated with the active drug and saline into the contralateral arm in random order. Bilateral infiltration lasted about 2 min. Capsaicin (100 µg, 20 µl) was injected into the centre of the pretreated skin of one arm 10 min after infiltration. In the first trial the injection of capsaicin was carried out 5 cm proximal to the wrist, and in the second trial the injection site was moved 1 cm proximal to the preceding injection site to prevent injection at the same site.

Experiment 2

This experiment was similar to experiment 1, but the skin at the injection site was pretreated by subcutaneous infiltration with ketamine hydrochloride 5.0 mg in 2.0 ml (Ketalar®, Warner-Lambert/Parke-Davis, Ballerup, Denmark) (pH=5.2) or 0.9% saline in 2.0 ml (NaCl. SAD) (pH=6.0). As in experiment 1, the contralateral arm was infiltrated with ketamine if the capsaicin site had been pretreated with saline and vice versa. Capsaicin was injected in one forearm 10 min after the skin had been pretreated. The site of injection of capsaicin was 7 cm proximal to the wrist in this first trial and was moved 1 cm more proximally in the second trial to prevent injection at the same site.

Tactile threshold

The same investigator (HG) carried out all measurements, in a quiet room (temperature 20–22°C) with the subject comfortably resting in a supine position. The tactile pain threshold (TPT) was measured on the forearm contralateral to the capsaicin injection site. It was defined as the least force necessary to bend a von Frey hair that was felt as painful. The TPT was determined before and 9 min after subcutaneous infiltration by bending a von Frey hair (Semmes–Weinstein monofilaments; Stoelting, IL, USA, graded from 0.004 to 446.68 g) on the skin at the subcutaneous infiltration site. The von Frey hairs were calibrated once at the start of the study, and the same von Frey hairs were used in both experiments.

Assessment of pain and hyperalgesia

Six radiating lines (60° between adjacent lines) from the injection site with ticks at 1 cm intervals were drawn on the skin before the start of the experiment. A point was marked 3 cm proximal to the injection site. Spontaneous and evoked pain intensities were measured using a VAS with a range of range 0–100, with 0=no pain and 100=unbearable pain. To assess brush-evoked pain, cotton gauze was swept back and forth three times at the 3 cm point at a speed of 1–2 cm s^{-1} and pain intensity was scored on a VAS. Punctate-evoked pain was assessed by bending a fixed von Frey hair (75.86 g) twice at the 3 cm point at a rate of 1 Hz, and was scored in a similar fashion. All measurements were done at specific time intervals and in the following order: (1) spontaneous pain intensity; (2) brush-evoked pain intensity; (3) punctate-evoked pain intensity; (4) area of brush-evoked hyperalgesia; (5) area of punctate-evoked hyperalgesia.

The area of brush-evoked hyperalgesia was assessed by moving a hand-held cotton gauze along each of the six radiating vector lines. starting in skin areas with normal sensation and moving towards the injection centre in 1 cm steps at a rate of approximately 1 cm s^{-1}. Subjects were asked to report when the sensation changed to a sensation of tenderness or pain. The area was calculated from the drawn hexagon.

The area of punctate-evoked hyperalgesia was assessed by bending a hand-held von Frey hair (75.86 g) towards the injection site in steps of 1 cm at a rate of 1 cm s^{-1}. Subjects were asked to report when the sensation became more painful. The area was calculated as described above.

Side-effects

Subjects were asked about side-effects at specific intervals. Reported side-effects were graded as weak, moderate or severe.

Statistical analysis

Statistical analysis was carried out using Jandel Sigmastat for Windows, version 2.0. The normality of the distribution of the data was tested with the Kolmogorov–Smirnov test. After the normal distribution of the data had been confirmed, the data were analysed by parametric methods. VAS scores for pain induced by subcutaneous injection of lidocaine, ketamine and saline were compared by the paired *t*-test in each experiment. TPTs before and after subcutaneous injection of saline, lidocaine and ketamine were analysed with the paired *t*-test. Data are presented as mean (SEM). Effect parameters were spontaneous capsaicin pain, pain evoked by brush and punctate stimuli, and areas of brush-evoked and punctate-evoked hyperalgesia. Differences in spontaneous pain, evoked pain and areas of hyperalgesia between treatment groups were analysed by parametric two-way analysis of variance with repeated measures (ANOVA RM) followed, in the case of significance, by multiple comparison using Dunnett's method. Data are presented as mean (SEM). *P*-values less than 0.05 were considered to be statistically significant.

Results

As a result of the randomization, seven subjects received capsaicin on different sides in experiments 1 and 2. Four subjects received capsaicin on the same side and one subject in each experiment participated in only one experiment.

There was a significant increase in the TPT (Table 1) after infiltration of lidocaine ($P<0.01$, paired *t*-test). Ketamine did not change the TPT, whereas saline increased it significantly ($P<0.05$, paired *t*-test) in experiment 2.

Mean VAS scores for spontaneous pain (Table 2) immediately after subcutaneous infiltration of lidocaine were significantly lower than after saline infiltration in experiment 1 ($P<0.01$, paired *t*-test). Mean VAS scores after subcutaneous infiltration of ketamine were significantly higher than those after saline infiltration in experiment 2 ($P<0.01$, paired *t*-test). There were no significant differences in mean VAS scores after subcutaneous saline in experiments 1 and 2. Pain induced by infiltration was short-lasting and disappeared in most cases before injection of capsaicin. Ketamine gave rise to slight pain when capsaicin was injected (VAS scores 7 and 8) in only two out of 24 subjects. Lidocaine gave rise to pain in one subject out of 24 (VAS score 28), whereas saline-induced pain ceased in all subjects before the injection of capsaicin.

Lidocaine, but not ketamine, reduced the VAS score for spontaneous pain induced by intradermal capsaicin significantly (ANOVA RM, $P<0.001$; Dunnett's test, $P<0.05$, lidocaine versus saline) (Fig. 1).

Table 1 Tactile pain threshold (TPT/g; mean (SEM)) *$P<0.05$ (paired *t*-test), before versus after subcutaneous infiltration ($n=12$)

	Before infiltration	After infiltration
Experiment 1		
Lidocaine	22.8 (5.4)	419.2 (18.2)*
Saline	23.5 (5.3)	33.0 (9.9)
Experiment 2		
Ketamine	55.1 (9.7)	67.1 (8.6)
Saline	95.4 (20.0)	117.4 (19.0)*

Table 2 VAS pain score (0–100) after subcutaneous infiltration of lidocaine, ketamine and saline. *$P<0.05$ (paired *t*-test), active drug versus saline

	VAS score (SEM)
Experiment 1	
Lidocaine	9 (2)*
Saline	20 (3)
Experiment 2	
Ketamine	26 (3)*
Saline	17 (2)

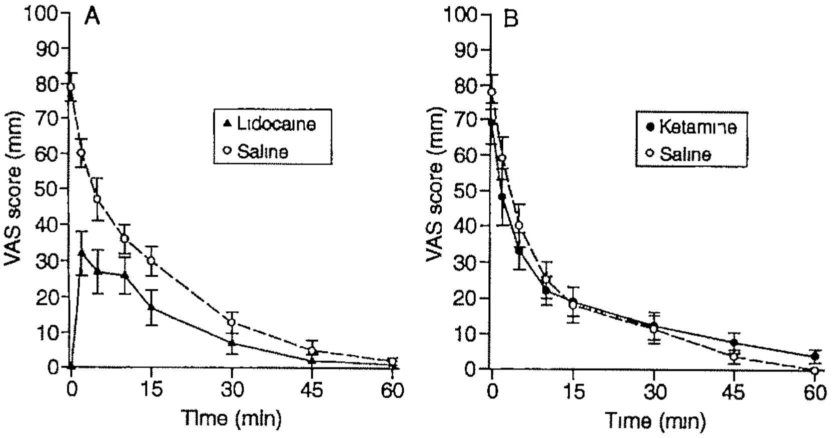

Fig 1 Spontaneous pain intensity plotted as mean VAS pain score±SEM. Pain was reduced by pretreating the capsaicin injection site with local s.c. infiltration of lidocaine (A), but s.c. infiltration of ketamine (B) did not reduce pain (ANOVA RM, $P<0.001$, $P<0.05$ lidocaine *vs* saline)

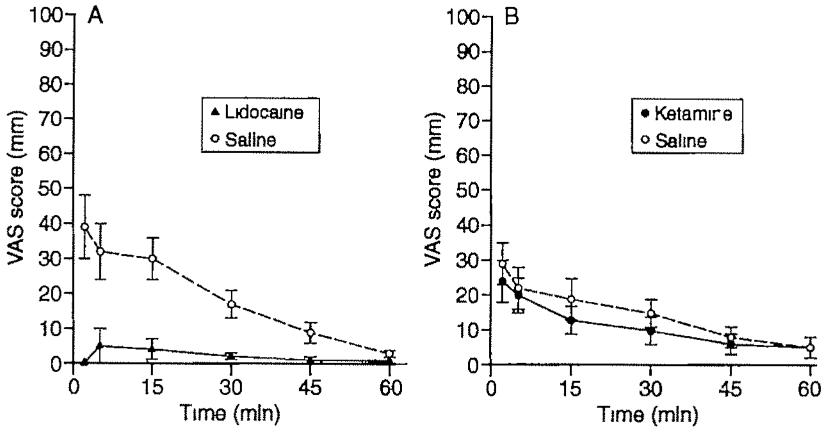

Fig 2 Brush-evoked pain intensity plotted as mean VAS pain score±SEM. Pain was reduced by pretreating the capsaicin injection site with local s.c. infiltration of lidocaine (A), but s.c. infiltration of ketamine (B) did not reduce pain (ANOVA RM, $P<0.001$, $P<0.05$ lidocaine *vs* saline).

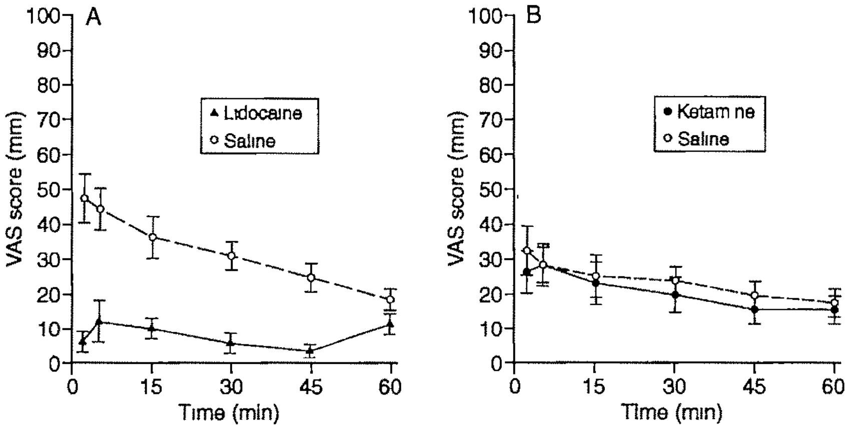

Fig 3 Punctate-evoked pain intensity plotted as mean VAS pain score±SEM. Pain was reduced by pretreating the capsaicin injection site with local s.c. infiltration of lidocaine (A), but s.c. infiltration of ketamine (B) did not reduce pain (ANOVA RM, $P<0.001$; $P<0.05$ lidocaine *vs* saline)

Lidocaine reduced the VAS score for brush-evoked pain significantly (ANOVA RM, $P<0.001$; Dunnett's test, $P<0.05$, lidocaine versus saline), whereas ketamine produced no effect on brush-evoked pain (Fig. 2).

The VAS score for punctate-evoked pain at the 3 cm point were reduced significantly by lidocaine (ANOVA RM, $P<0.001$; Dunnett's test, $P<0.05$, lidocaine versus saline). The effect of ketamine was similar to saline (Fig. 3).

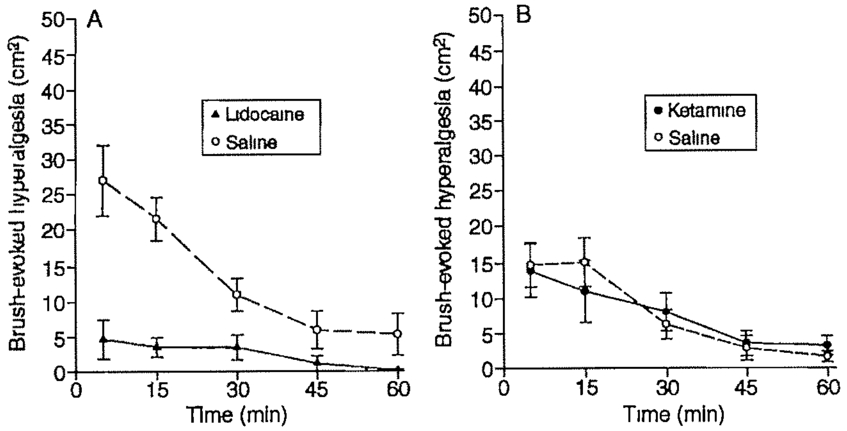

Fig 4 The area of brush-evoked hyperalgesia (mean±SEM) was reduced by pretreatment of the capsaicin injection site with local s.c. infiltration of lidocaine (A), but s.c. infiltration of ketamine (B) did not reduce the area (ANOVA RM, $P<0.001$; $P<0.05$ lidocaine *vs* saline).

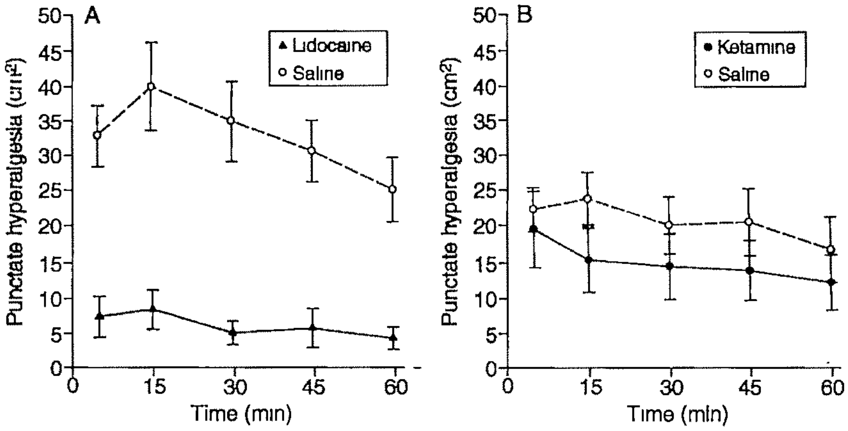

Fig 5 The area of punctate-evoked hyperalgesia (mean±SEM) was reduced by pretreating the capsaicin injection site with local s.c infiltration of lidocaine (A), but s.c. infiltration of ketamine (B) did not reduce the area (ANOVA RM, $P<0.001$; $P<0.05$ lidocaine *vs* saline)

Lidocaine, but not ketamine, reduced the area of brush-evoked hyperalgesia significantly (ANOVA RM, $P<0.001$; Dunnett's test, $P<0.05$, lidocaine versus saline) (Fig. 4).

Lidocaine reduced the area of punctate-evoked hyperalgesia significantly, whereas ketamine had no effect (ANOVA RM, $P<0.001$; Dunnett's test, $P<0.05$, lidocaine versus saline) (Fig. 5).

Because 11 of 12 subjects participated in both trials, it was possible to look for systemic effects of ketamine and lidocaine. There were no differences in capsaicin-induced pain and evoked pain scores when the capsaicin injection site was pretreated with saline and the contralateral injection was of either ketamine or lidocaine. Mean values of both brush-evoked pain (ANOVA RM, $P=0.33$) and punctate-evoked pain tended to be lower when the contralateral side was pretreated with ketamine than when it was treated with lidocaine, although the difference did not reach significance (Fig. 6).

There were no differences in mean areas of brush-evoked and punctate-evoked hyperalgesia when the side contralateral to the capsaicin site was pretreated with ketamine or lidocaine. Mean areas of brush-evoked hyperalgesia (ANOVA RM, $P=0.20$) and punctate-evoked hyperalgesia (ANOVA RM, $P=0.21$) tended to be lower when ketamine was injected contralateral to the capsaicin site than when lidocaine was injected, but none of the differences reached significance (Fig. 7).

Lidocaine and saline produced no side-effects, whereas paraesthesia, dizziness and sleepiness were seen in six out of 24 cases (25%) after ketamine. Side-effects occurred 5–10 min after subcutaneous injection and lasted up to 30 min.

Discussion

Hyperexcitability has peripheral and central components, and it is well established that central hyperexcitability is mediated partly by NMDA receptor-linked systems.[1 3–6 30] The recent anatomical demonstration of NMDA receptors in the peripheral nervous system in animals has raised the possibility that peripheral NMDA receptors, in addition to centrally located NMDA receptors, are involved in pain and hyperalgesia.[20–22 31] Using a burn injury model, Warncke

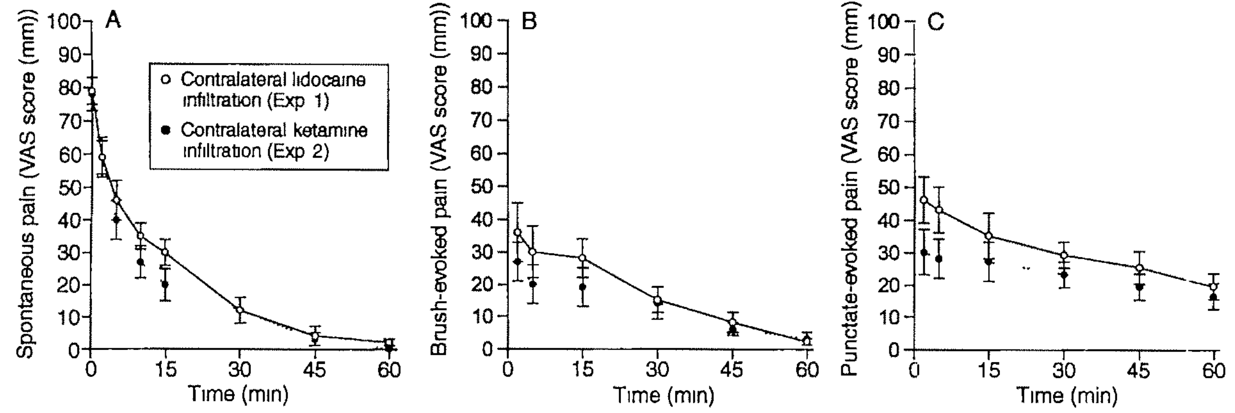

Fig 6 The effects of local infiltration of lidocaine and ketamine contralateral to the capsaicin injection site on VAS pain scores (mean±SEM) Placebo (saline) was injected at the capsaicin injection site (A) Spontaneous pain (B) Brush-evoked pain (C) Punctate-evoked pain.

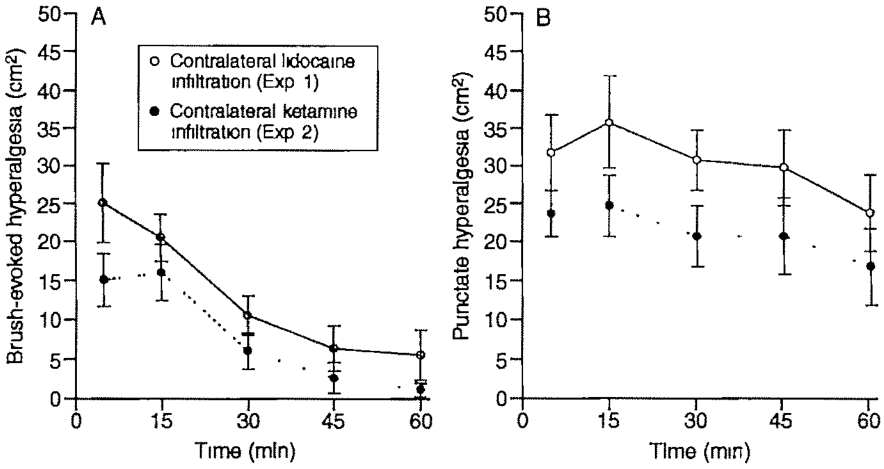

Fig 7 The effects of local s c infiltration of lidocaine and ketamine contralateral to the capsaicin injection site on the area of hyperalgesia (mean±SEM). Placebo (saline) was injected at the capsaicin injection site. (A) Brush-evoked hyperalgesia. (B) Punctate-evoked hyperalgesia.

and colleagues[23] found that the non-competitive NMDA receptor antagonist ketamine blocked the development of punctate hyperalgesia and wind-up phenomena. In a similar human burn injury model, Pedersen and colleagues[24] showed that ketamine had a transient antinociceptive effect. In the present study, using a capsaicin model, we failed to find an effect on pain and secondary hyperalgesia after local infiltration of the skin with ketamine before injury. Our finding confirms the observations of others.[32] Hence, under these conditions peripheral NMDA receptor systems do not seem to be involved in pain and hyperalgesia. In contrast to the effect of ketamine, local infiltration of lidocaine into the skin before injury blocked spontaneous pain and evoked pain and almost abolished areas of hyperalgesia, indicating that the capsaicin model is a sensitive model and is amenable to modulation by a peripherally acting agent.

All three treatments (ketamine, lidocaine and saline) had a slight pain-inducing effect after skin infiltration. Lidocaine produced the lowest and ketamine the highest pain rating, but all mean pain scores were below 30 and the pain disappeared after a few minutes. Thus, it is unlikely that the different effects of ketamine and lidocaine on hyperalgesia found in this study can be explained by different pain-inducing effects of each treatment. Similarly, it is unlikely that the different pain response produced by each treatment could have violated the blinding of the study, because saline was used as a separate control in both experiments and saline gave rise to a mean VAS pain rating between 17 and 20. Furthermore, all pain scores were in the lower third of the VAS scale, precluding the possibility that the subjects and examiner distinguished between the treatments.

In accordance with previous studies,[27] infiltration with lidocaine increased TPT while infiltration with ketamine did not change TPT. Previous reports on tactile thresholds in the burn injury model differ. Warncke and colleagues[23] found unchanged tactile thresholds after local infiltration with ketamine. This finding was in contrast to the increased tactile thresholds reported by Pedersen and colleagues.[24] Differences in pain models, dosage and timing of injury and ketamine may explain this discrepancy. In experiment 2, saline increased TPT. The reason for elevation in the pain threshold is unclear, but a DNIC (diffuse noxious inhibitory controls) effect[33 34] is a possibility. Alternatively, it is possible that the assessment was done in a slightly different area. Some variation in TPT between experiments 1 and 2 before subcutaneous infiltration seems to be present. In experiment 1 the first injection site was 5 cm proximal to the wrist. The injection site was moved 1 cm at each session in order to prevent injection at the same site. It is therefore unlikely that desensitization of the skin can account for the difference in TPT found in the present study. A prolonged effect of subcutaneous lidocaine is also an unlikely explanation for the difference in TPT, because the subcutaneous injection evoked a pain score similar to that reported by others.[24] It is possible that the skin closer to the wrist is more sensitive to punctate stimuli than more proximal skin.

Locally administered lidocaine inhibits afferent nerve conduction, including nociceptor activity.[35] In the present study, secondary hyperalgesia was almost abolished by lidocaine. This observation is in line with earlier findings reported by LaMotte and colleagues[3] in the capsaicin model and with later observations in the burn injury model.[23 27] The peripheral activation required to develop hyperalgesia is not clear. The observation that both brush and punctate hyperalgesia were abolished despite ongoing pain suggests that a prerequisite for secondary hyperalgesia is an afferent nociceptive drive of sufficient magnitude to generate secondary hyperalgesia (in this case punctate- and brush-evoked hyperalgesia). Our findings are in contrast to findings reported by Cervero and colleagues,[36] who observed the development of mechanical hyperalgesia to punctate and stroking stimuli after the application of prolonged non-painful heat stimuli in healthy subjects, whereas others suggest that hyperalgesia to brush but not punctate stimuli depend critically on persistent nociceptive activity of C fibres.[2 37]

In addition to its opioid interaction[38] and sodium channel-blocking properties,[39 40] ketamine also has affinity for the NMDA receptor complex, where it exerts a non-competitive block. Experimental[12 13 15 17] and clinical[10 11 14 16] studies have clearly documented the ability of systemically administered ketamine to block various manifestations of central sensitization. Previous studies have suggested that peripherally administered ketamine, with an action that is presumably limited to the periphery, can also block pain and sensitization.[23 24] The failure to see an effect of peripherally administered ketamine in the present study is in accordance with a preliminary report by Koppert and colleagues[32] in the capsaicin model, but at variance from those reported by others in a burn model.[23 24] The explanation for the transient reduction in spontaneous pain[24] and more prolonged reduction of evoked pain[23] and the failure to see an effect in the present study is not clear. However, there are important differences between these studies. First, differences in the method of eliciting pain and hyperalgesia is one possibility. Mild painful heat stimuli activate C-mechano-heat (CMH) nociceptors.[41] The increased nociceptive input induces central sensitization, which is reflected in secondary hyperalgesia to mechanical stimuli. In contrast, capsaicin activates capsaicin-sensitive CMH nociceptors and capsaicin-sensitive Aδ primary sensory neurones, and a recent study suggests that punctate hyperalgesia is mediated by capsaicin-insensitive Aδ-fibres.[42] These findings suggest that the mechanisms underlying the central sensitization induced by burn injury and capsaicin may be different. We measured four parameters of secondary hyperalgesia (scores for pain evoked by brush and punctate stimuli and areas of brush- and punctate-evoked hyperalgesia) and did not find any effect of ketamine. In the study by Warncke and colleagues,[23] in which punctate-evoked hyperalgesia and wind-up-like pain were reduced, pain was induced in both calves simultaneously, but it may be difficult to distinguish stimuli when pain is felt in two regions. Their design was sensitive to a systemic effect of ketamine. Since saline-treated injuries were compared directly with ketamine-treated injuries in the same session, the effect observed may be systemic as well as peripheral. With the present study design, it was possible to control for a systemic effect of ketamine by comparing capsaicin-induced hyperalgesia in two separate sessions.

It may be argued that a reduced capsaicin response with repeated dosing and lack of counterbalance influenced the present results. We consider this unlikely. Capsaicin injections and drug infiltration were moved 1 cm in each session to prevent injection into the same site. In a recent study, we found an unchanged capsaicin response after repeated doses.[43] Finally, the pain intensity in experiment 2 was similar to that reported by Pedersen and colleagues.[24] It may be argued that the greater area of hyperalgesia induced by capsaicin injected into saline-pretreated skin in the lidocaine group than by injection into saline-pretreated skin in the ketamine group may have biased our results in favour of lidocaine. Our study design was sensitive to a systemic effect of ketamine, and we suggest that the smaller area induced in saline-pretreated skin in the ketamine group may have been caused by the systemic effect of ketamine. Despite an almost similar VAS score in the two sessions in experiment 2, one possibility is that local treatment with ketamine 5 mg may produce a systemic plasma concentration that is not sufficient to reduce the intense pain induced by capsaicin but is adequate to reduce the manifestations of central hyperexcitability.

In our study, dizziness, paraesthesia and sleepiness were reported in 25% of all cases after local ketamine, symptoms that are similar to those reported after i.v. ketamine.[10 12 14 16 17] No subjects reported side-effects in the study by Warncke and colleagues,[24] but in the study by Pedersen and colleagues[24] the frequency of side-effects was high. Our dose of ketamine was similar to the dose used by Warncke and colleagues,[23] whereas a higher dose was used by Pedersen and colleagues,[24] which may explain the higher frequency of side-effects in the latter study. It is unlikely that the lack of effect of ketamine in our study can be explained by the use of a dose of ketamine that was too low, because it was sufficient to produce slight systemic side-effects. Furthermore, we did find a reduction, albeit insignificant, in capsaicin-induced pain and hyperalgesia in skin pretreated with saline and ketamine contralaterally to the capsaicin site compared with lidocaine contralateral to the capsaicin site. Taking these results together, it is likely that in the capsaicin model peripherally administered ketamine exerts its antinociceptive and antihyperalgesic actions by a systemic mechanism when it is injected s.c.

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Remifentanil inhibits muscular more than cutaneous pain in humans

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In experimental studies, drug-induced analgesia is usually assessed by cutaneous stimulation. If analgesics act differently on cutaneous and deep nociception, the results of these studies may not be entirely applicable to clinical pain involving deep structures. We tested the hypothesis that opioids have different abilities to inhibit cutaneous and muscular pain. Either the opioid remifentanil or placebo was infused in 12 healthy volunteers in a cross-over fashion. Repeated electrical stimulation (five impulses at 2 Hz) was applied to both skin and muscle. Pain thresholds were recorded. Remifentanil caused a higher increase in the muscular pain thresholds than in the cutaneous pain thresholds (P=0.035). We conclude that opioids inhibit muscular pain more strongly than cutaneous pain in humans.

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In experimental human studies, the analgesic effect of drugs is usually assessed by applying nociceptive stimuli to the skin.[1] However, in most clinical pain conditions, pain also arises from deep structures. If analgesics act differently on cutaneous and deep nociception, the results of studies exploring only cutaneous pain may not be entirely applicable to clinical pain involving deep structures. Recently, a model for inducing muscle pain by electrical stimulation has been developed.[2] So far, no human study has compared the effects of an analgesic on cutaneous and muscular pain.

In this randomized, placebo-controlled, crossover study on healthy volunteers, we compared the effects of the opioid μ-agonist remifentanil on cutaneous and muscular pain.

Methods

The study was approved by the local ethics committee. The exclusion criteria were pregnancy, hypersensitivity to opioids, the use of any analgesic drug during the last 2 weeks, drug or alcohol abuse, and a history of the use of psychotropic drugs. Twelve healthy volunteers (five females) were enrolled after they had given written informed consent. Their age was 23.8 (21–31) yr and the body weight 70 (SD 9) kg.

Medication

Each volunteer was tested in two sessions at the same time of the day, with an interval of at least 4 days. In each session, either remifentanil or saline 0.9% was administered in a randomized, double-blind fashion Remifentanil or saline was administered as a computer-controlled intravenous infusion using a Harvard 22 infusion pump (Harvard Apparatus, Edenbridge, Kent, UK). The pump was driven by the software Stanpump (S. Schafer, Palo Alto, CA, USA), which attempts to reach and maintain constant target plasma concentrations. Minto's pharmacokinetic values[3] were used. Plasma concentrations of remifentanil of 1 and 2 ng ml^{-1} were targeted stepwise, even when the syringe contained saline. These concentrations were chosen because they are below the ranges used previously for conscious sedation.[4]

General procedure

All the experiments were performed by the same investigator. For each volunteer, all the tests were applied to the same side of the body (selected randomly) in both the remifentanil and the placebo session. Baseline recordings (0 target plasma concentration) were preceded by a training

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session to make the volunteer familiar and comfortable with the testing procedure. The test series at 1 and 2 ng ml^{-1} were performed 10 min after the target concentration of remifentanil had been changed. Immediately before each test series, sedation was assessed using a 10 cm visual analogue scale (0=fully fit, 10=hardly able to keep the eyes open).

Cutaneous stimulation

Two bipolar surface Ag–AgCl electrodes (Dantec, Skovlunde, Denmark) were placed on the skin of the foot, 1 cm distal to the lateral malleolus for elicit cutaneous electrical stimulation.[5] The electrode surface was 7×4 mm and the distance between the two electrodes was 1.5 cm. A train of five square-wave impulses was delivered from a computer-controlled constant current stimulator (University of Aalborg, Aalborg, Denmark). Each of these impulses lasted 1 ms. The duration of the train of five impulses totalled 25 ms, so they were perceived as a single stimulus. This stimulus train was repeated five times at the same intensity, at a frequency of 2 Hz (i.e. every 0.5 s).[5] The current intensity was increased stepwise until the pain threshold was identified. The pain threshold was defined as the minimum stimulus intensity eliciting a subjective increase in perception during the five stimulations, so that the last one or two impulses were perceived as painful. Repeated stimulation was preferred to stimulation with a single electrical stimulus because it has proven more reliable for investigating the analgesic effect of drugs and is not influenced by sedation.[6]

Muscular stimulation

Two 28 G, 3 cm long insulated needle electrodes, with 3 mm long uninsulated tips, were used for the electrical stimulation of muscles (Dantec). The needles were inserted 2 cm into the tibialis anterior muscle, 14 cm distal to the middle of the patella and 2 and 2.5 cm lateral to the lateral edge of the tibia respectively.[2] Because the needle was insulated, concomitant skin stimulation was prevented. Repeated electrical stimulation was performed as described for cutaneous stimulation to determine the pain threshold.

For both cutaneous and muscular stimulation, if the threshold was above a maximal current of 80 mA the threshold was defined as 80 mA. The mean of three threshold determinations was used for the data analysis.

Data analysis

All the data were analysed by the Friedman repeated measures analysis of variance on ranks. The effect of remifentanil on the pain thresholds was analysed by considering the differences between remifentanil and placebo measurements for each individual at each target plasma concentration. To analyse the differential effect on cutaneous and muscular stimulation, the differences between muscular and cutaneous thresholds for each subject at each target plasma concentration were considered. This analysis was performed separately for the placebo and the remifentanil sessions. A P value less than 0.05 was considered as significant.

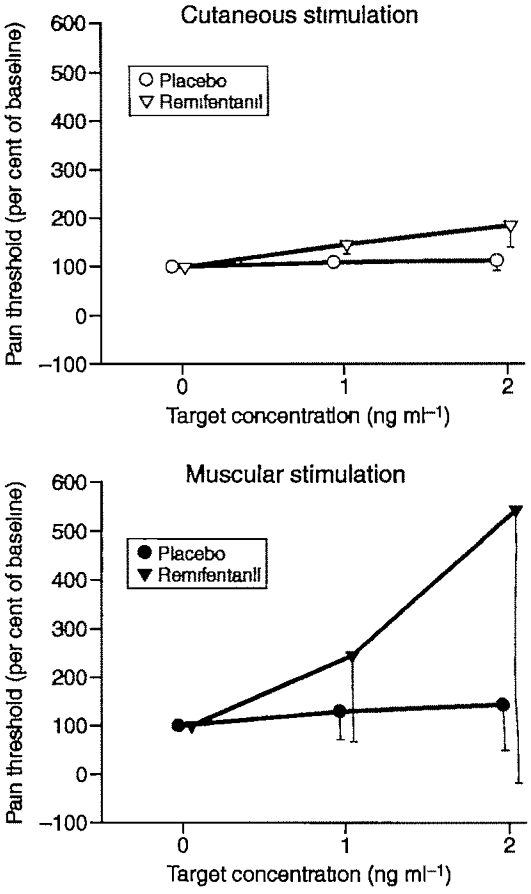

Fig 1 Pain thresholds after repeated electrical stimulation of skin (top) and muscles (bottom) Data (mean and SD) are percentages of baseline recordings. Target concentration 0 represents the baseline recordings, made before starting the infusion pump In the placebo sessions, the infusion pump was set to reach target plasma concentrations of remifentanil of 1 and 2 ng ml^{-1}, but the syringe contained saline instead of remifentanil Administration of remifentanil resulted in significantly higher pain thresholds than placebo after both cutaneous (P<0.001) and muscular (P=0.039) stimulation. Remifentanil caused a higher increase in the thresholds after muscular stimulation than after cutaneous stimulation (P=0.035).

Results

Blinding was frequently incomplete, mostly because of the remifentanil-induced sedation. The mean values of the sedation scores in the remifentanil sessions at target plasma concentrations of 0, 1 and 2 ng ml^{-1} were 1.6 (SD 1.2), 4.5 (2.2) and 6.6 (3.0) respectively. All the subjects were fully cooperative for the experiment.

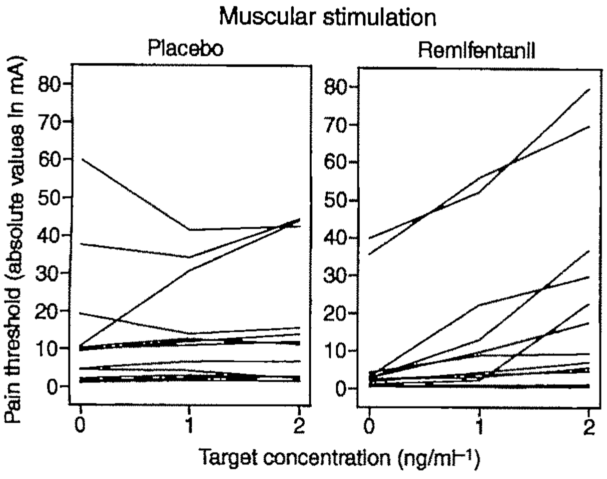

Fig 2 Pain thresholds for each volunteer after repeated electrical stimulation of muscles Absolute data are presented.

The results pertaining to the pain thresholds are presented in Fig. 1. Compared with placebo, remifentanil resulted in significantly higher pain thresholds after both cutaneous ($P<0.001$) and muscular ($P=0.039$) stimulation. Placebo affected cutaneous and muscular pain thresholds to the same extent. In contrast, remifentanil caused a higher increase in the thresholds after muscular stimulation than in the thresholds after cutaneous stimulation ($P=0.035$).

Data pertaining to each volunteer for muscular stimulation are presented in Fig. 2.

Discussion

This is the first study comparing the pharmacological modulation of cutaneous and muscular pain in humans. We found that the opioid μ-agonist remifentanil is more effective in inhibiting muscular pain than cutaneous pain.

Animal studies have demonstrated the presence of descending pathways in the spinal cord that are activated by opioidergic supraspinal mechanisms and inhibit the peripheral nociceptive input to spinal cord neurones.[7] These opioidergic mechanisms are much more effective in inhibiting deep than cutaneous nociception.[7]

There is much evidence that analgesics have different actions on responses to different types of nociceptive stimuli, probably because different stimuli evoke different pain mechanisms.[6 8–10] Depending on the stimulus applied, a drug can vary in efficacy. For instance, propofol increases the threshold of the nociceptive reflex to single stimulation (indicating an analgesic effect), but does not affect the threshold of the nociceptive reflex to repeated stimulation (indicating no analgesic effect) and reduces pain tolerance of mechanical pressure (indicating a hyperalgesic effect).[6] Isoflurane[11] and extradural local anaesthetics[8 12] more easily inhibit pain induced by single stimuli than pain evoked by repeated stimuli. This is the result of addition of synaptic potentials in the spinal cord neurones during repeated stimulation, which may ultimately lead to an increased neuronal response (temporal summation of nociceptive stimulation).[5] In contrast, NMDA (*N*-methyl-D-aspartate) antagonists strongly decrease pain threshold after repeated nociceptive stimulation but have no effect on pain threshold after a single stimulus.[13] This evidence indicates that the analgesic effect of drugs should be investigated by multimodal testing procedures.[1] Methods investigating the mechanisms involved in clinical pain, such as inflammation,[14] hyperalgesia[15] and temporal[5] and spatial[16] summation, have been used in human studies in an attempt to reduce the gap between experimental and clinical pain.

The new finding of the present study is a further step in the improvement of experimental models. Because analgesics may have different actions on cutaneous and deep pain and because deep pain is involved in most clinical pain conditions, the use of deep pain models is likely to improve the reliability of experimental pain studies. Therefore, the concept of multimodal testing procedure can be extended to the concept of multimodal–multistructure testing, in which nociception arising from different body structures is explored.

In order to apply the same stimulus to skin and muscle, we chose electrical stimulation as the experimental model. Additional methods of inducing muscle pain include the injection of hypertonic saline[17] or algogenic substances, such as bradykinin, serotonin and substance P.[18 19] Pain thresholds after electrical stimulation of muscles were characterized by wide variability, as shown by the high standard deviations (Fig. 1). This was the result of wide interindividual variability, whereas the response within the experimental session was reproducible for most volunteers (Fig. 2).

In conclusion, we provide evidence for a difference in the abilities of analgesics to affect cutaneous and muscular pain in humans. Muscle stimulation is more effective than cutaneous stimulation in detecting opioid-induced analgesia. These findings, together with the clinical importance of muscle pain, support the wide use of muscle pain models in human studies. The combination of cutaneous and muscular pain models may be a valuable new tool in the preclinical evaluation of analgesics in humans.

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Comparison of alfentanil, fentanyl and sufentanil for total intravenous anaesthesia with propofol in patients undergoing coronary artery bypass surgery†

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We have studied the pharmacokinetics and pharmacodynamics of alfentanil, fentanyl and sufentanil together with propofol in patients undergoing coronary artery bypass graft surgery (CABG). Sixty patients (age 40–73 yr, 56 male) were assigned randomly to receive alfentanil, fentanyl or sufentanil and propofol. Plasma concentrations of these drugs and times for the plasma concentration to decrease by 50% (t_{50}) and 80% (t_{80}) after cessation of the infusion were determined. Times were recorded to awakening and tracheal extubation. Total dose and plasma concentrations of propofol were similar in all groups. Mean total doses of alfentanil, fentanyl and sufentanil were 443, 45 and 4.4 $\mu g\ kg^{-1}$, respectively. Time to awakening did not differ significantly. In patients receiving fentanyl, the trachea was extubated on average 2 h later than in those receiving sufentanil and 3 h later than in those receiving alfentanil ($P<0.05$). The t_{80} of fentanyl was longer ($P<0.05$) than that of alfentanil or sufentanil, and there was a linear correlation between the t_{80} of the opioid and the time to tracheal extubation ($r=0.51$; $P<0.01$). However, the t_{50} values for these opioids were similar and did not correlate with recovery time. In conclusion, patients undergoing CABG and who were anaesthetized with fentanyl and propofol needed mechanical ventilatory support for a significantly longer time than those receiving alfentanil or sufentanil and propofol. On the basis of the interindividual variation observed, the time to tracheal extubation was most predictable in patients receiving alfentanil and most variable in patients receiving fentanyl, a finding which may be important if the patients are transferred to a step-down unit on the evening of the operation.

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Intravenous hypnotics and opioids play an important role in cardiac anaesthesia. For 'fast-track' recovery to be achieved, the patient must recover rapidly from the high plasma concentrations reached during cardiac anaesthesia. The interaction between opioids and propofol in reducing the Cp_{50} (the plasma concentration that will prevent a response in 50% of patients for a given stimulus) of propofol, and that between opioids and isoflurane in reducing minimum alveolar concentration (MAC) has been defined and is very similar for both propofol and isoflurane and the opioids. The initial decrease in Cp_{50} and MAC is very steep, but a plateau is reached above an opioid concentration equivalent to 250–400 ng ml^{-1} of alfentanil, 4–6 ng ml^{-1} of fentanyl or 0.4–0.6 ng ml^{-1} of sufentanil.[1]

In planning fast-track recovery from a cardiac procedure that is associated with very intense stimuli, it is prudent to administer the opioids to achieve these ceiling concentrations and then titrate the hypnotic or volatile anaesthetic as

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needed during the procedure.[1] Studies using this method and comparing alfentanil, fentanyl and sufentanil together with propofol are lacking. Therefore, we have studied the pharmacokinetics and pharmacodynamics of these three opioids in total intravenous anaesthesia (TIVA) with propofol in patients undergoing coronary artery bypass graft surgery (CABG).

Methods

The study design was double-blind and randomized for three groups. On the basis of our experience of time to tracheal extubation (which was regarded as the primary endpoint of recovery from the anaesthetic), it was calculated that 20 patients would be required in each group to demonstrate a 50% difference in time to tracheal extubation at a level of significance of $P=0.05$ and power of 80%. We obtained institutional approval to study 60 patients undergoing elective CABG. None of the patients, when presented with the informed consent form, refused to participate in the study. Exclusion criteria were left ventricular ejection fraction less than 40%, significant valvular dysfunction, renal or liver insufficiency, uncontrolled hypertension, treatment with any known inhibitor or inducer of the cytochrome P4503A enzymes,[2] morbid obesity, anaesthesia duration more than 6 h, and reoperation due to any complication.

Routine medication was terminated the evening before surgery, except for beta blockers and long-acting nitrates, which were given concomitantly with the premedication. Aspirin was halted 1 week before surgery. Two hours before induction of anaesthesia, the patients received orally administered lorazepam 40 μg kg^{-1}.

Our target plasma concentrations were 400 ng ml^{-1} for alfentanil, 6 ng ml^{-1} for fentanyl and 0.6 ng ml^{-1} for sufentanil. The dosage of alfentanil was adjusted from that of our previous study;[2] fentanyl and sufentanil were administered on the assumption that equipotent doses (mg kg^{-1}) of alfentanil, fentanyl and sufentanil are approximately 10:1:0.1.[3 4] The syringes containing alfentanil 500 μg ml^{-1}, fentanyl 50 μg ml^{-1} or sufentanil 5 μg ml^{-1} were prepared by our hospital pharmacy just before induction of anaesthesia. The basic infusion rate of propofol was chosen to avoid intraoperative awareness[5] and the infusion rate could be increased over a wide range to prevent arousal in response to noxious stimulation.[6] All the staff in the operating room and in the intensive care unit (ICU) remained unaware of the randomization code of the patients.

Before induction of anaesthesia, peripheral venous and radial arterial cannulae were inserted. The systolic arterial blood pressure (SAP) was recorded 3–5 min after insertion of the radial arterial cannula. Anaesthesia was induced with alfentanil 75 μg kg^{-1}, fentanyl 7.5 μg kg^{-1} or sufentanil 0.75 μg kg^{-1}, and propofol 1.0–1.5 mg kg^{-1}. The induction dose of propofol was given concomitantly with the opioid within 3 min in order to mask the different onset time of alfentanil compared with those of fentanyl and sufentanil.[3 4] All patients received ephedrine 10 mg at the beginning of induction to avoid hypotension.[7] At the beginning of induction, continuous infusions were started of propofol 100 μg kg^{-1} min^{-1} and alfentanil 1.5 μg kg^{-1} min^{-1}, fentanyl 0.15 μg kg^{-1} min^{-1} or sufentanil 0.015 μg kg^{-1} min^{-1}. The rate of opioid infusion was maintained unchanged until skin closure.

Before skin incision, a bolus dose of propofol 0.5 mg kg^{-1} was given, and the infusion rate was increased to 150 μg kg^{-1} min^{-1}. Thereafter, the infusion rate of propofol was adjusted between 100 and 250 μg kg^{-1} min^{-1} in steps of 50 μg kg^{-1} min^{-1} to maintain the SAP between 90 and 130 mmHg. During CPB, the rate of propofol was allowed to fall to 50 μg kg^{-1} min^{-1}. During the time when the infusion rate of propofol was being increased, a bolus dose of 0.5 mg kg^{-1} was always given. Outside the range of the propofol infusion rate, haemodynamic control was provided by bolus doses of nitroglycerin 0.05 mg, ephedrine 5 mg or norepinephrine 5 μg. Rocuronium 1 mg kg^{-1} was given for muscle paralysis, with additional bolus doses as needed. After endotracheal intubation, the lungs were ventilated with a mixture of oxygen in air. All patients received a slow injection of tranexamic acid 20 mg kg^{-1} before initiation of CPB.

All surgical procedures were performed under moderate hypothermia (nasopharyngeal temperature 33–34°C). A cold crystalloid cardioplegic solution was used. During CPB, the pump flow rate was 2.4 l min^{-1} m^{-2} and perfusion pressure 50–80 mmHg. Before separation from CPB, all patients were rewarmed (nasopharyngeal temperature 37°C, bladder temperature ≥36°C) and an infusion of epinephrine 0.04 μg kg^{-1} min^{-1} was started. After surgery, the patients were warmed actively with a forced-air warmer until awake. In case of gagging on the intubation tube or agitation, the patient was sedated with a bolus dose of propofol 20 mg. The time to awakening was defined as the time to the return of appropriate responses to the command 'Move your right and left arm and your legs' and to the question 'Do you feel any pain?'. Ketorolac 20 mg was administered intravenously 60 min after the end of anaesthesia and 6 and 14 h thereafter. After awakening, additional analgesia was provided by intravenous bolus doses of morphine 0.05 mg kg^{-1}.

Separation from mechanical ventilation was initiated when the patient was awake and calm. We used the same weaning protocol and extubation criteria as in our previous study with CABG patients:[2] according to the end-tidal carbon dioxide concentration (E'_{CO_2}) and the arterial carbon dioxide tension (Pa_{CO_2}), mandatory ventilations were reduced, allowing the E'_{CO_2} and the Pa_{CO_2} to increase to 7% and 6.5 kPa, respectively. Simultaneously, with increasing spontaneous ventilatory rate, the mandatory ventilation was reduced until the patient was breathing in the presence of 5 cm H_2O of continuous positive airway pressure. Extubation criteria were as follows: the patient was breathing on continuous positive airway pressure (FI_{O_2} <0.40) with the ventilation rate less than 20; arterial oxygen tension was more than 9.8 kPa; and Pa_{CO_2} was less than 6.5 kPa. The Pa_{CO_2} was recorded just before extubation and 30 min thereafter. In every patient, the postoperative care, the weaning process and tracheal extubation were performed by the same anaesthetist (J.A.).

To determine drug plasma concentrations, arterial blood samples were drawn before induction of anaesthesia, 10 min after induction, every 30 min thereafter until initiation of CPB, 15 min after initiation of CPB (from the CPB circuit), at the end of CPB (from the CPB circuit), every 30 min thereafter until skin closure, and at the end of anaesthesia (skin closure). After anaesthesia, blood samples were drawn every 30 min for 3 h, every 60 min for an additional 3 h, and at 12, 15, 18, 21 and 24 h. Plasma concentrations of alfentanil, fentanyl and propofol were determined for all samples. Sufentanil determinations had to be restricted because of the limitation of resources for analysis (before induction, 10 min thereafter, at the end of anaesthesia, and thereafter from all samples until 15 h).

Plasma concentrations of alfentanil and fentanyl were determined by capillary column gas-liquid chromatography.[8] Tioridazine was used as the internal standard. The sensitivity of the method for alfentanil was 10 ng ml^{-1} and that for fentanyl was 0.1 ng ml^{-1}. The intra-assay coefficient of variation for alfentanil was 11.1% at 110 ng ml^{-1} (n=8) and the day-to-day CV was 3.5% at 140 ng ml^{-1} (n=11). The intra-assay and day-to-day CVs for fentanyl were 5.0% at 5.8 ng ml^{-1} (n=5) and 6.6% at 2.0 ng ml^{-1} (n=13), respectively. Plasma concentrations of sufentanil were determined by radioimmunoassay.[9] The limit of quantification for sufentanil was 0.020 ng ml^{-1}. The intra-assay CVs for sufentanil were 7.3% at 0.041 ng ml^{-1} (n=2) and 2.7% at 0.544 ng ml^{-1} (n=2). The day-to-day CVs were 4.4% at 0.041 ng ml^{-1} (n=2) and 5.1% at 0.412 ng ml^{-1} (n=2). Plasma concentrations of propofol were determined by high-performance liquid chromatography.[10] Thymol was used as the internal standard. The limit of quantification for propofol was 0.5 μg ml^{-1}, the calibration curve was linear (r^2=0.996) over the concentration range of 0.5–10 μg ml^{-1}, and the intra-assay and day-to-day CVs were 0.6–5.4%. Plasma concentrations of alfentanil and fentanyl were determined at the Department of Biomedicine, University of Helsinki, those of sufentanil at the Janssen Research Foundation, and those of propofol at Bioanalytics, Research and Development, Leiras Inc.

The pharmacokinetics of alfentanil, fentanyl and sufentanil were characterized by the time after cessation of the infusion for the drug plasma concentration to decrease by 50% (t_{50}) and 80% (t_{80}), and by the terminal elimination half-life ($t_{\frac{1}{2}}$). The t_{50} and t_{80} values were determined by interpolation using the logarithmic plasma concentration–time profile for each patient. The elimination rate constant (k_{el}) was determined by regression analysis of the log-linear part of the curve. The $t_{\frac{1}{2}}$ was calculated from $t_{\frac{1}{2}}$=ln 2/k_{el}. In every patient, the mean plasma concentration of alfentanil, fentanyl or sufentanil during anaesthesia was calculated from the samples drawn at 10 min and at the end of anaesthesia. The plasma concentrations of the opioid at time of awakening and at tracheal extubation were interpolated from the logarithmic plasma concentration–time profile for each patient. For propofol, the area under the drug plasma concentration–time profile (AUC) during anaesthesia was calculated using the logarithmic trapezoidal rule. The t_{50} for propofol was determined, as was the plasma concentration of propofol at time of awakening. The t_{80} for propofol could not be determined, since this concentration remained below the detection limit. At the time of extubation, propofol was not detectable.

CABG with CPB is associated with profound physiological changes that may alter the pharmacokinetics of intravenous anaesthetics.[11] Therefore, we recorded the amount of all crystalloids administered during CPB, urine excretion and bleeding until 24 h, and the greatest weight gain during the hospital stay. Furthermore, we recorded the fraction of MB creatine kinase (CK-MB) at 24 h. The day of discharge to the ward was noted. We do not have a 'step-down' unit, and the patients were transferred to the ward according to the routine policy of our cardiac ICU, which handles 1500 adult surgical patients a year. Because many patients were transferred to other hospitals after 4–5 days and these hospitals have different criteria for home readiness, the length of hospital stay was not recorded.

Statistical analysis

Results are expressed as mean and SD. Patient characteristics were compared by analysis of variance and the χ^2 test. The pharmacokinetic and pharmacodynamic parameters between the groups were compared by analysis of variance and a posteriori testing was done with Tukey's test. The Pearson product-moment correlation coefficient was used to investigate the relationship between t_{50} and t_{80} for the opioids and t_{50} for propofol and for time to awakening and tracheal extubation. All the data were analysed with Systat for Windows, version 5.0 (Systat, Evanston, IL, USA).

Results

Patient characteristics are shown in Table 1. Eight of the 60 patients who were initially enrolled had to be excluded because of violation of the study protocol, so eight additional patients were enrolled. One patient (alfentanil) was excluded because of improper delivery of the study drug, one patient (fentanyl) because infusion of diltiazem[2] had been started, and two patients (alfentanil, sufentanil) because anaesthesia lasted more than 6 h. Two patients were excluded because of reinstitution of cardiopulmonary bypass (CPB) during the same sternotomy: one (alfentanil) because of uncontrolled bleeding from a posterior anastomosis, and one (sufentanil) because of bleeding from a tear

Table 1 Preoperative characteristics (mean value (SD) or number of patients (n)). NYHA=New York Heart Association; MI=myocardial infarction, LV=left ventricle; ACE=angiotensin-converting enzyme *Significant differences between groups ($P<0\ 05$)

	Alfentanil	**Fentanyl**	**Sufentanil**
Patients (n)	20	20	20
Male/female	19/1	18/2	19/1
Age (yr)	58 (40–73)	62 (41–72)	61 (48–72)
Weight (kg)	75 (9)	77 (8)	80 (9)
Smokers (non/ex/still) (n)	10/5/5	7/10/3	8/10/2
NYHA functional class 2/3	12/8	12/8	14/6
Previous MI (n)	9	10	10
LV ejection fraction (%)	58 (11)	58 (13)	58 (14)
Preoperative therapy (n)			
Beta blocker	20	20	20
Long-acting nitrate	17	15	17
Aspirin*	20	14	18
ACE inhibitor	4	5	4

Table 2 Perioperative medication and surgical data (mean value (SD) or number of patients (n)). SAP=invasive systolic blood pressure, CPB=cardiopulmonary bypass; CK-MB=MB-fraction of creatine kinase, IU=international unit, ICU=intensive care unit, POD=postoperative day

	Alfentanil	**Fentanyl**	**Sufentanil**
Patients (n)	20	20	20
Lorazepam premedication (μg kg^{-1})	49 (9)	44 (8)	45 (7)
SAP before anaesthetic (mm Hg)	133 (7)	134 (9)	135 (12)
Propofol (mg kg^{-1})	27 8 (6.5)	29 8 (8 0)	28.4 (5 7)
Opioid (μg kg^{-1})	443 (48)	45.2 (5.3)	4.43 (0.55)
Propofol between end of anaesthesia and awakening: no. patients	6	4	6
mg per patient	24 (9)	23 (5)	41 (26)
Morphine between awakening and extubation (mg)	10 (7)	8 (7)	9 (6)
Morphine until 24 h (mg)	24 (9)	17 (11)	19 (8)
Aortic cross-clamping (min)	54 (15)	59 (17)	63 (19)
CPB (min)	83 (21)	84 (21)	90 (24)
Anaesthesia (min)	247 (31)	251 (35)	247 (36)
Crystalloids during CPB (ml)	4150 (750)	4000 (600)	4350 (700)
Urine excretion until 24 h (ml)	4470 (1030)	3860 (670)	4480 (970)
Bleeding until 24 h (ml)	670 (160)	760 (260)	770 (300)
CK-MB (IU) at 24 h	28 (31)	32 (42)	47 (61)
From ICU to ward			
First POD (n)	18	13	16
Second POD (n)	2	5	3
Third POD (n)		2	1
Weight gain on third POD (kg)	2.0 (1.5)	2.3 (1.8)	1 7 (2.1)

in the pulmonary artery. One patient (fentanyl) underwent resternotomy because of bleeding, and one (fentanyl) had to be sedated with an infusion of propofol for a few hours after awakening because of failure to tolerate the endotracheal tube and inability to breathe spontaneously.

The three groups were similar with respect to their characteristics (except for use of aspirin), premedication, severity of coronary artery disease, preanaesthetic SAP, duration of anaesthesia, duration of aortic cross-clamping and duration of CPB (Tables 1 and 2). At skin incision or sternotomy, five patients receiving alfentanil, 11 receiving fentanyl and four receiving sufentanil required one or two bolus doses of nitroglycerin because of hypertension.

Plasma concentration–time profiles of the opioids are presented in Figures 1 and 2. The mean plasma concentration of alfentanil at awakening was 44 (SD 13)% of that at the end of anaesthesia, that of fentanyl was 36 (13)% and that of sufentanil was 34 (7)%. At tracheal extubation, plasma concentrations of alfentanil, fentanyl and sufentanil were 18 (8)%, 20 (10)% and 17 (5)% of that at the end of anaesthesia, respectively (Table 3). Time to awakening did not differ significantly between the groups, whereas in patients receiving fentanyl, the trachea was extubated on average 2 h later ($P<0.05$) than in those receiving sufentanil and 3 h later ($P<0.01$) than in those receiving alfentanil (Fig. 3 and Table 3). On the basis of the interindividual variation observed, time to tracheal extubation was most predictable in patients receiving alfentanil and most variable in patients receiving fentanyl (Fig. 3). The t_{50} values of alfentanil, fentanyl and sufentanil did not differ significantly, nor did they correlate with recovery. However, the t_{80} of fentanyl was significantly ($P<0.05$) longer than those of alfentanil and sufentanil (Table 3), and the t_{80} of the opioid was significantly correlated with time to tracheal extubation in all groups ($r=0.51$; $P<0.01$). No differences between the groups were detected in Pa_{CO_2} before extuba-

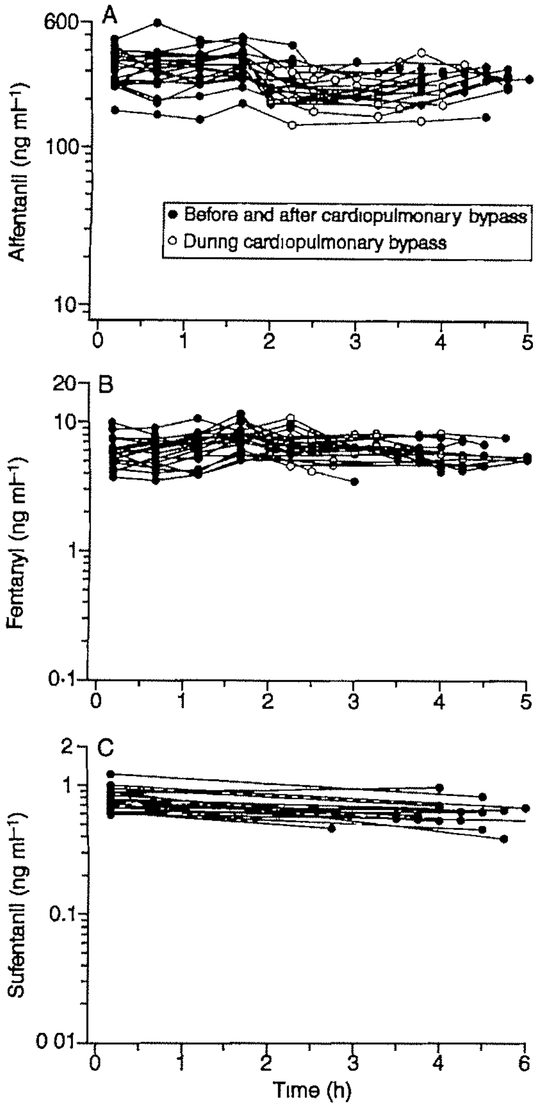

Fig 1 Plasma concentrations of alfentanil (A), fentanyl (B) and sufentanil (C) during anaesthesia for coronary artery bypass surgery (n=20, all groups) Sufentanil determinations were restricted because of limited resources for analysis

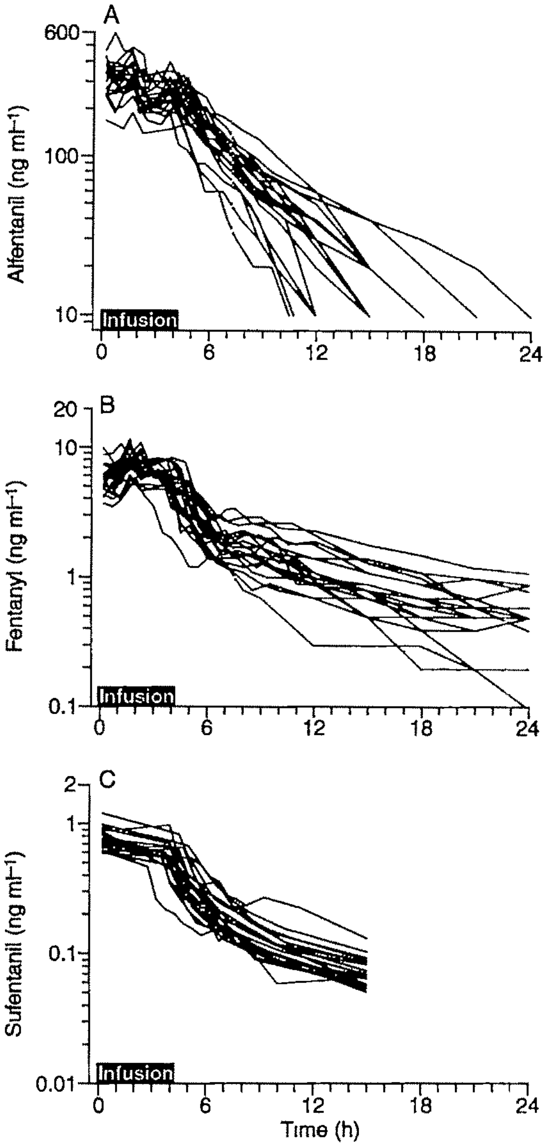

Fig 2 Plasma concentrations of alfentanil (A), fentanyl (B) and sufentanil (C) during and after coronary artery bypass surgery (n=20, all groups) Infusion=average duration of the anaesthetic.

tion or thereafter (Table 3), or in the consumption of morphine (Table 2). The $t_{\frac{1}{2}}$ of fentanyl was significantly longer than that of sufentanil or alfentanil and the $t_{\frac{1}{2}}$ of sufentanil was significantly longer (P<0.05) than that of alfentanil (Table 3). No linear correlation existed between the $t_{\frac{1}{2}}$ values of the opioids and recovery.

Plasma concentration–time profiles of propofol are presented in Figure 4. The total dose, AUC, and t_{50} of propofol were similar in all three groups (Table 4). The short t_{50} of propofol did not correlate with recovery. Between the end of anaesthesia and awakening, the number of patients receiving bolus doses of propofol and the cumulative dose of propofol did not differ significantly between the groups (Table 2).

The amount of all crystalloids administered during CPB, urine excretion and bleeding until 24 h, CK-MB at 24 h, length of ICU stay and greatest weight gain during the hospital stay were similar in all three groups (Table 2).

Discussion

The similar consumption and AUC of propofol in our CABG patients receiving alfentanil, fentanyl or sufentanil suggests that the opioid doses, selected on the basis of their equipotent electroencephalographic effects in volunteers[3 4] were also equipotent with respect to clinical anaesthetic potency, which allows reliable comparison of recovery characteristics between the groups. A similar potency ratio was recently reported in CABG patients receiving fentanyl or sufentanil supplemented with isoflurane.[12] In these patients, mean plasma concentrations of 7.3 ng ml^{-1} for

Table 3 Pharmacokinetic and pharmacodynamic values of alfentanil, fentanyl and sufentanil (mean (SD)). CANE=mean plasma concentration during anaesthesia; CAWA=plasma concentration at awakening, CEXT=plasma concentration at tracheal extubation *Significantly different from patients receiving alfentanil or sufentanil ($P<0.05$) †Significantly different from that receiving alfentanil ($P<0.05$)

	Alfentanil	**Fentanyl**	**Sufentanil**
Pharmacokinetics			
t_{50} (min)	102 (34)	92 (78)	69 (25)
t_{80} (min)	310 (72)	494 (230)*	329 (97)
$t_{\frac{1}{2}}$ (min)	164 (58)	449 (136)*	373 (48)†
CANE (ng ml^{-1})	300 (60)	5.7 (1.2)	0.690 (0.127)
CAWA (ng ml^{-1})	120 (50)	1.9 (0.7)	0.208 (0.051)
CEXT (ng ml^{-1})	50 (30)	1.1 (0.4)	0.103 (0.025)
Pharmacodynamics			
Time to awakening (min)	138 (66)	214 (161)	167 (61)
Time to extubation (min)	355 (80)	541 (220)*	422 (131)
Pa_{CO_2} before extubation (kPa)	6.1 (0.6)	6.2 (0.5)	6.1 (0.5)
Pa_{CO_2} 30 min after extubation (kPa)	6.1 (0.5)	6.3 (0.5)	6.2 (0.5)

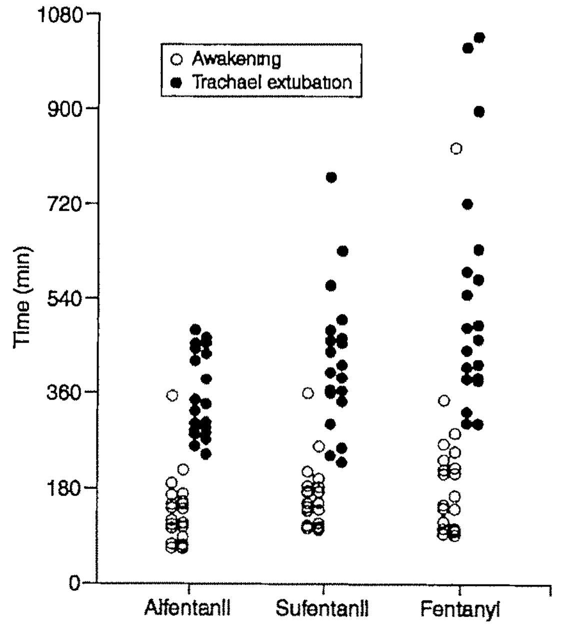

Fig 3 Time to awakening (open circles) and tracheal extubation (filled circles) after alfentanil, sufentanil or fentanyl together with propofol (n=20, all groups).

fentanyl and 0.71 ng ml^{-1} for sufentanil were on the steep part of the concentration–response relationship, whereas those of 13.2 ng ml^{-1} and 1.25 ng ml^{-1}, respectively, were on the plateau. This finding is in good agreement with the ceiling plasma concentrations targeted in our patients.[1] In the present study, the t_{80} of fentanyl was significantly longer than those of alfentanil and sufentanil and there was a linear correlation between the t_{80} of the opioids and time to tracheal extubation. The t_{50} values of these opioids were similar and were not correlated with time to awakening or tracheal extubation. Compared with the opioids, propofol was cleared rapidly and probably did not influence recovery.

In our patients, the observed 50 and 80% decrement times differed from the modelled context-sensitive decrement times for these three opioids.[13 14] The elimination of

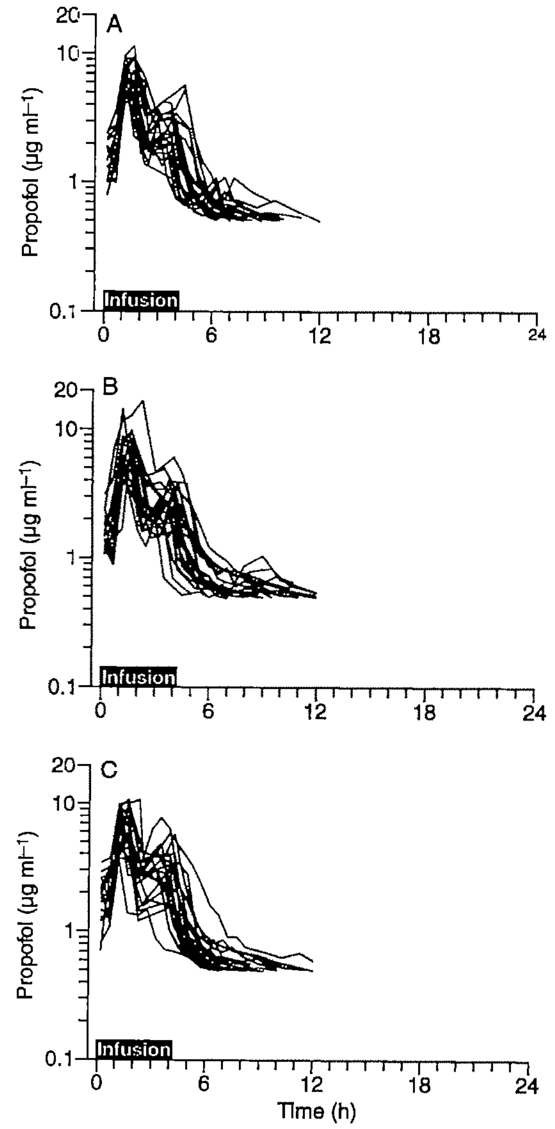

Fig 4 Plasma concentrations of propofol in patients receiving alfentanil (A), fentanyl (B) and sufentanil (C) during and after coronary artery bypass surgery (n=20, all groups). Infusion=average duration of anaesthesia.

Table 4 Pharmacokinetic values of propofol (mean (SD)) CAWA=plasma concentration at awakening

	Alfentanil group	Fentanyl group	Sufentanil group
Propofol			
t_{50} (min)	26 (6)	30 (9)	32 (15)
CAWA (μg ml^{-1})	0.68 (0.15)	0.64 (0.10)	0.63 (0.10)
AUC (μg ml^{-1} h)	13.4 (4.1)	14.8 (6.8)	14.5 (4.7)

fentanyl was faster than predicted and no differences were detected between alfentanil and sufentanil. However, instead of a computer-controlled infusion scheme to reach the target concentrations,[13] we chose the clinically more widely used loading dose followed by a zero-order infusion, and in contrast to the model[13] we determined the t_{50} and t_{80} values of the drugs by interpolation using the logarithmic plasma concentration–time profile for each patient. Furthermore, the complex effect of CPB on the pharmacokinetics of intravenous anaesthetics[11] probably explains, at least in part, the differences between the modelled and observed values. In our patients receiving alfentanil or fentanyl, the loading dose followed by a zero-order infusion resulted in a stable plasma concentration of the opioid until the initiation of CPB. Thereafter, the plasma concentrations of these opioids decreased slightly. However, during CPB the unbound fraction of the opioid is increased,[15] and in clinical practice the infusion rate of the opioid is not increased to keep the total plasma concentrations stable.

Time to awakening did not differ significantly. The t_{50} values of the opioids and that of propofol were not correlated with times to awakening and tracheal extubation. In patients having conventional CABG with CPB, time to awakening can also be affected by factors not associated with the anaesthetics. For instance, brain swelling after surgery[16] may influence recovery. In the present study, the relative decrease in drug plasma concentration up to the time of tracheal extubation was approximately 80% for all three opioids. After TIVA with propofol in patients undergoing general surgery lasting for about 5 h, the relative decrease in drug plasma concentration up to the time of tracheal extubation was 48% for alfentanil and 62% for sufentanil. Unfortunately, the t_{50} values of the opioids and propofol were not determined.[17] Again, factors not related to the anaesthetic, such as brain swelling and changes in homeostasis, may explain the obvious difference between patients undergoing general surgery and CABG with CPB. The sensitivity of the time to extubation as a measure of recovery from the opioid effect was probably improved by our rigorous weaning and extubation protocol, which was also used in our previous study with CABG patients.[2] The postoperative care, the weaning process, and the tracheal extubation of the patients were performed by the same anaesthetist. There were no differences between the groups in Pa_{CO_2} values just before and after extubation.

Drug interactions can influence the times needed to return to consciousness and spontaneous ventilation. In female patients undergoing lower abdominal surgery, a pharmacodynamic interaction between propofol and alfentanil reduced the alfentanil requirement. On the other hand, alfentanil decreased the plasma concentration of propofol associated with the return of consciousness.[18] Because the consumption and the plasma concentrations of propofol were similar in our study groups, it can be concluded that alfentanil, fentanyl and sufentanil were administered in equipotent doses. Because the decrease in the plasma concentration of propofol after anaesthesia was also similar and rapid in all three groups, it is plausible that the pharmacodynamic interaction between propofol and the opioids did not influence recovery. Propofol inhibits dose-dependently the oxidative metabolism of alfentanil and sufentanil *in vitro*.[19] However, although the dosage of alfentanil in the present study was based on our previous study using alfentanil without propofol,[2] plasma concentrations of alfentanil remained lower than predicted. Moreover, elimination of alfentanil in the present study was similar to that observed after anaesthesia with infusions of alfentanil and midazolam supplemented with isoflurane.[2] Although clinical studies with sufentanil are lacking, it is unlikely that the pharmacokinetic interaction between propofol and the opioids would have affected our patients' recovery.

Theoretically, the observed differences in times to awakening and tracheal extubation could have been affected by pharmacokinetic or pharmacodynamic interactions between lorazepam and the opioids. Alfentanil, fentanyl and sufentanil are metabolized in the liver by the enzyme cytochrome P450 3A4.[20 21] Lorazepam, however, is metabolized by hepatic conjugation to glucuronic acid, which is a non-microsomal reaction and is not affected by changes in cytochrome P450 activity.[22] Furthermore, because alfentanil, fentanyl and sufentanil are equivalent μ-agonists, it is plausible that lorazepam potentiates the effects of the opioids on the central nervous system in a similar manner.[23]

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Clinical comparison of 'single agent' anaesthesia with sevoflurane versus target controlled infusion of propofol

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The introduction of total intravenous anaesthesia (TIVA) and the use of volatile induction/maintenance anaesthesia (VIMA) has led to the rediscovery of 'single agent' anaesthesia, eliminating the transition phase from induction to maintenance. We compared quality, patient acceptability and cost of TIVA using target control infusion (TCI) with propofol and VIMA with sevoflurane. Forty patients undergoing spinal surgery of 1–3 h were assigned to one of two groups. Group I received propofol–air–oxygen for induction followed by propofol–air–oxygen for maintenance. Group II received 8% sevoflurane–oxygen for induction and sevoflurane–oxygen–nitrous oxide for maintenance. Propofol had a significantly faster mean (SD) induction time (67 (20) s) than sevoflurane (97 (38) s) but was associated with double the incidence of involuntary movements. Although not significant, twice the number of interventions by the anaesthetist were required to maintain an adequate level of anaesthesia in the sevoflurane group. Emergence times, characteristics, postoperative nausea, vomiting and pain were unaffected by the anaesthetic technique. However, a more predictable emergence time was found following sevoflurane. Cardiovascular stability was good and comparable in both groups. The majority of patients found either technique acceptable and would choose the same anaesthetic again. Induction and maintenance was substantially cheaper with sevoflurane (£28.06) compared with propofol (£41.43).

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Intravenous (i.v.) agents are used commonly for induction of anaesthesia followed by inhalational agents for maintenance. A problem with this technique is the transition phase from induction to maintenance. The rapid redistribution of the i.v. agent could lead to lightening of the anaesthetic before an adequate depth is attained with the inhalational agent. This has promoted the rediscovery of 'single agent' anaesthesia, which avoids problems associated with a transition phase.[1]

Propofol is a short acting general anaesthetic agent used widely for total i.v. anaesthesia (TIVA) because of its favourable induction properties and rapid clearance. Its antiemetic properties are well acknowledged, but it is associated with pain on injection and cardiovascular and respiratory depression.[2]

The introduction of the target control infusion (TCI) system has enabled relatively accurate dosing by continuous infusion, based on the pharmacokinetic profile of propofol in an average patient.[3] This convenient system makes TIVA with propofol an attractive option with the benefit of minimal pollution to the operating room environment.

Sevoflurane, a relatively new short acting inhalational agent has a blood:gas partition coefficient of 0.69 permitting greater control and ability to change anaesthetic depth. It is also non-irritant and pleasant smelling making it much more acceptable for induction of anaesthesia compared with other inhalational agents such as isoflurane, desflurane and enflurane.[4] The availability of this non-pungent and rapid acting anaesthetic makes it an attractive option for volatile induction/maintenance anaesthesia (VIMA).

There have been several studies comparing propofol with sevoflurane for induction, maintenance, and recovery. However, TIVA (i.e. no nitrous oxide) using TCI with propofol *vs* VIMA with sevoflurane has not yet been compared, especially in the clinical setting of major surgery in conjunction with opioids such as morphine.

The aim of this study was to compare 'single agent' anaesthesia with sevoflurane with target controlled infusion of propofol. The primary objectives were to evaluate the speed of induction and recovery, and the haemodynamic differences between the two techniques.

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Patients and methods

The approval of the hospital's Research Ethics Committee was obtained. In order to detect a difference in the mean change in heart rate (HR) of 5 beats min^{-1} between the groups (α=0.05, β=0.2), 15 patients were required in each group. After written informed consent, a total of 40 patients (ASA I–II) of both sexes, age range 25–80 yr, were enrolled onto the study. All patients were scheduled to undergo elective spinal surgery of 1–3-h duration. Patients with a history of cardiovascular, respiratory, hepatic, renal or neurological disease and those who were pregnant or had received a general anaesthetic within the previous 2 weeks, were excluded from the study.

Patients were assigned randomly to one of two groups (numbers out of an envelope). Group I (*n*=20) received propofol for induction followed by propofol–air–oxygen for maintenance. Group II (*n*=20) received sevoflurane–nitrous oxide–oxygen for both induction and maintenance of anaesthesia. All anaesthetics were administered by consultants. Preoperative medication of temazepam 10 mg was administered on the ward, at the discretion of the anaesthetist, before induction of anaesthesia. A large vein on the patient's forearm was cannulated.

In the anaesthetic room, all patients received an initial loading dose of up to 10 mg morphine i.v. and 100% oxygen via a face mask for 2–3 min prior to induction. Thereafter alfentanil at a maximum of 4 mg h^{-1} as an i.v. bolus to supplement anaesthesia was administered intraoperatively.

Sevoflurane was administered with a Blease vaporizer (Blease Medical Equipment Ltd, Chesham, UK), and propofol with a Graseby 3500 infusion pump (Sims Graseby Ltd, Watford, UK). In Group I, the patient's age and weight was entered into the TCI unit enabling so target propofol concentrations to be set and the infusion started. Target induction concentrations were 4–6 μg ml^{-1} and anaesthesia was maintained with propofol (4–8 μg ml^{-1}), along with air and oxygen. Group II patients were induced using a face mask with sevoflurane in a circle system starting at 8% with an initial fresh gas flow of 6 litre min^{-1} decreasing to a total gas flow of 3 litre min^{-1} during maintenance (67% nitrous oxide in oxygen) with up to 3.5% sevoflurane. After paralysis with a bolus of atracurium 0.4–0.6 mg kg^{-1} i.v., and tracheal intubation, the lungs were ventilated to normocapnia throughout the procedure. The end-tidal sevoflurane concentration and the propofol maintenance target infusion were adjusted as necessary to maintain an adequate depth of anaesthesia as judged by clinical signs and haemodynamic responses to surgical stimuli. Once this was achieved, delivery of either anaesthetic was kept constant. Residual neuromuscular block was pharmacologically antagonized at the end of surgery with neostigmine 2.5 mg and glycopyrrolate 0.5 mg when necessary. A local infiltration of 0.5% bupivacaine with adrenaline was applied to the incision site at the start of the procedure.

At the end of surgery, sevoflurane and nitrous oxide, or propofol were discontinued abruptly and the lungs were ventilated with 100% oxygen at a flow rate of at least 6 litre min^{-1}. After discontinuation of the anaesthetic, patients were asked repeatedly in a normal tone of voice to open their eyes until an appropriate response was obtained. The trachea was extubated when a regular spontaneous breathing pattern had been re-established and when patients were able to open their eyes on command.

In the anaesthetic room, ECG, pulse oximetry and non-invasive blood pressure monitoring were applied to all patients. Mean arterial pressure (MAP) and HR were recorded 2–3 min prior to induction of anaesthesia (baseline), and then again at predetermined times; pre- and post-intubation, pre- and post-incision, pre-extubation and after admission to recovery room. In addition, highest and lowest MAP and HR, the administration of any vasoactive drugs and intraoperative anaesthetic interventions were noted for each group. Time intervals were recorded including induction (start of anaesthetic to loss of eye lash reflex), intubation (start of anaesthetic to intubation), spontaneous eye opening (end of anaesthetic to eye opening), extubation (end of anaesthetic to extubation), and orientation (end of anaesthetic to until the patient stated his or her name, birth date and ward number). All adverse effects associated with induction such as involuntary movements, coughing, breath holding, restlessness, laryngospasm and pain on injection were noted.

On admission to the recovery room, patients were evaluated for orientation, assessed for nausea and vomiting on a scale 0–3 (none, mild, moderate, severe) and their level of pain noted using scores 0–5 (none, mild, moderate, severe, very severe, worst possible). When orientated fully, patients were asked to assess the acceptability of induction anaesthesia. They were asked about the smell of the volatile gas and also about pain of injection of the i.v. drug. Induction of anaesthesia was rated as 'pleasant', 'neither pleasant nor unpleasant' or 'unpleasant'. Finally, patients were asked if they would be happy to receive the same anaesthetic again. The above observations were made by the same investigator who questioned all the patients.

Total costs of anaesthesia per operation were calculated based on the current UK list price of liquid sevoflurane (250 ml), 1% propofol prefilled syringe (50 ml), and disposables (cannulae, manometer lines and syringes) (Appendix).

Data were analysed using the Microsoft Excel (version 6.0) and Origin (version 4.1) statistical package. Parametric data were analysed using paired and non-paired *t*-tests with Bonferoni corrections for multiple comparisons. Discrete data were analysed using chi-square. All values are represented as mean (SD) with statistical significance determined at $P<0.05$.

Table 1 Patient characteristics, duration of anaesthesia and drug requirements Values are mean (SD) [95% CI] *P<0 05 between groups

	Propofol		Sevoflurane	
Sex (M/F)	12/8		11/9	
Age	52 (35–77)	[50 4–53 6]	54 (28–75)	[52 4–55 6]
Weight (kg)	78 (13)	[76 4–79.6]	78 (9)	[76 7–79 3]
Surgical duration (min)	106 (39)	[103 3–108 7]	111 (41)	[108 2–113 8]
Anaesthetic duration (min)	137 (38)	[134 3–139 7]	142 (53)	[138.8–145 2]
Morphine (mg)	9 7 (1.1)	[9 1–10 3]	9 5 (1 4)	[9–10]
Alfentanil (mg)	2 2 (1.3)	[1 7–2 7]	0 3 (0 8)*	[0–0 7]
Temazepam	8/20		6/20	

Table 2 Side effects during induction of anaesthesia No differences between the groups were detected

	Propofol	Sevoflurane
Involuntary movements	6 (30%)	3 (15%)
Coughing	0 (0%)	2 (10%)
Breath holding	1 (5%)	5 (25%)
Restlessness	0 (0%)	2 (10%)
Laryngospasm	0 (0%)	0 (0%)
Pain on injection	2 (10%)	0 (0%)

Results

There was no significant difference between the two groups with respect to patient characteristics, mean duration of surgery or anaesthetic time. Similar amounts of morphine were administered to both groups, but patients in the propofol group received significantly more alfentanil intraoperatively (mean 2.2 (SD 1.3) mg *vs* 0.3 (0.8) mg, P<0.0001) (Table 1).

Time to loss of consciousness after induction with propofol was significantly shorter than sevoflurane (66.7 (20.1) s (95% CI (64.7–68.7)) *vs* 96.9 (38) s (94.2–99.6)) (P=0.004), although there was no marked difference in intubation times (5.2 (1.4) min (4.7–5.7) *vs* 6 (1.3) min (5.5–6.5)).

Following administration of propofol and sevoflurane, involuntary movements were relatively common, occurring in 30 and 15% of patients, respectively. Two patients (10%) receiving propofol complained of pain on injection. Inhaled induction with sevoflurane was not associated with laryngospasm. However, two patients (10%) experienced slight respiratory irritation eliciting coughing. Five patients (25%) in the sevoflurane group exhibited breath holding (not sufficient to cause a Sa_{O_2} of <97% as measured by the pulse oximeter) and two (10%) demonstrated restlessness. Side effects and complications occurring during induction of anaesthesia are summarized in Table 2. Ephedrine 9 mg was administered on one occasion in each group.

HR and MAP recorded immediately before induction of anaesthesia (baseline) were similar in both groups, along with the highest and lowest HR and MAP recorded perioperatively (Table 3).

Table 3 Haemodynamic variables Values are mean (SD) [95% CI] No differences between the groups were detected

	Propofol		Sevoflurane	
Heart rate (beats min^{-1})				
Baseline	84 (13)	[82.4–85 6]	82 (17)	[80 2–83 8]
Highest (intraop)	89 (16)	[87 2–90 8]	91 (17)	[89 2–92.8]
Lowest (intraop)	63 (11)	[61 5–64 5]	61 (10)	[59 6–62 4]
MAP (mm Hg)				
Baseline	95 (14)	[93.4–96 6]	98 (15)	[96 3–99 7]
Highest (intraop)	100 (18)	[98 1–101 9]	94 (21)	[92–94]
Lowest (intraop)	59 (10)	[57 6– 60 4]	55 (10)	[53 6–56 4]

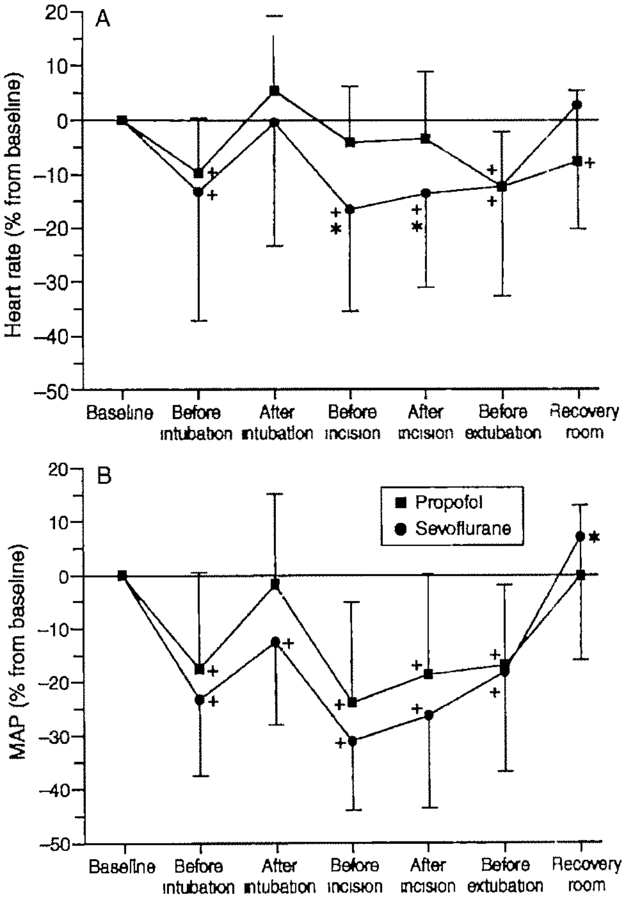

Fig 1 Changes in HR (A) and MAP (B) for the propofol (n=20) and sevoflurane (n=20) from before anaesthesia (baseline) and at specified times. Actual baseline values for HR are 84 (13) beats min^{-1} (mean (SD)) and 82 (17) beats min^{-1}, and baseline values for MAP are 95 (14) and 99 (15) mm Hg for the propofol and sevoflurane groups, respectively. Each point represents the mean (SD) percentage from baseline ^{+}P<0 05, from baseline, *P<0.05, between groups.

Induction was associated with a significant decrease in HR and MAP (between 10 and 23%) (Fig. 1). Tracheal intubation produced a transient increase towards baseline values in both HR and MAP and, in the period prior to skin incision, there was a significant decrease in MAP, in both groups. HR also decreased, but significantly more so in the sevoflurane group both pre- and post-incision. During the

Table 4 Emergence times, emergence complications, and recovery events Values are mean (SD) [95% CI]. No statistical significance between groups †Nausea and vomiting scores (0–3); ††pain scores (0–5)

	Propofol	**Sevoflurane**
Time to eye opening (min)	11.5 (5.3) [10.5–12.5]	11.1 (3.3) [10.3–11.9]
Time to extubation (min)	13.2 (6.5) [12.1–14.3]	12.3 (3.0) [11.5–13.1]
Time to stating name (min)	15.5 (6.1) [14.5–16.5]	15.5 (3.1) [14.7–16.3]
Emergence side effects		
Coughing	6 (30%)	4 (20%)
Breath holding	2 (10%)	1 (5%)
Restlessness	1 (5%)	1 (5%)
Shivering	1 (5%)	1 (5%)
Recovery events	Nausea and vomiting†	Pain††
	0 1 2 3	0 1 2 3 4 5
Propofol	19 1 0 0	7 11 2 0 0 0
Sevoflurane	17 2 1 0	8 8 4 0 0 0

remainder of the procedure, sevoflurane produced similar changes in HR and MAP values when compared with propofol (Fig. 1).

The time from discontinuation of the anaesthetic to spontaneous eye opening, extubation and to stating name and date of birth correctly were similar in both groups and there were no differences in subsequent recovery events (Table 4). The number of interventions made by the anaesthetist to adjust anaesthetic depth were 2.8 (0.9) (2.4–3.2) *vs* 6 (3.1) (5.2–6.8) for propofol and sevoflurane, respectively.

Two cases (10%) of mild and one case (5%) of moderate nausea were reported in the sevoflurane group, with only a single incidence reported in the propofol group. Pain scores were low with no difference between the two groups (Table 4).

Based on the amount of drug used, the cost of induction and maintenance of anaesthesia with sevoflurane was significantly cheaper than propofol (£28.06 (8.56) (£25.73–30.38) compared with £41.43 (18.85) (£39.53–43.33), respectively (P=0.001)). Additional costs (disposables) were only associated with the propofol group (£2.78).

The majority of patients (55% of the propofol group and 50% of the sevoflurane group) rated induction as 'pleasant'. The others were indifferent (neither pleasant nor unpleasant), barring two cases (10%) where induction was described as unpleasant, one from each group. Finally, a large proportion of patients in both groups stated a willingness (95% in each group) for receiving the same anaesthetic in the future.

Discussion

A number of studies have compared single-agent anaesthesia with i.v. propofol (not TCI) and sevoflurane.[5–7] This study demonstrates that for patients undergoing spinal surgery of up to 3 h duration, single-agent based anaesthesia with TCI propofol or sevoflurane is satisfactory when used together with opiates as in the normal clinical setting.

Previous investigations where either the maximum delivery of sevoflurane was 5% (limited by the vaporizer) or sevoflurane was administered in stepwise increments of 0.5% have reported induction times of between 109 and 186 s.[5 6 8 9] The ability to administer up to 8% sevoflurane has allowed for a more rapid induction of 84 s.[7] The induction time of the sevoflurane group reported in this study confirms this finding, having a similar time (97 s) despite using morphine at induction.

Induction with sevoflurane was associated with breath holding in 25% of the patients. However, this was not severe enough to cause hypoxaemia, as monitored by pulse oximetry, and a smooth induction was still attained, although breath holding may have prolonged induction. Two patients experienced coughing despite i.v. morphine pre-administration, and there were two cases of restlessness reported, which were not apparent in the propofol group.

Induction with both sevoflurane and propofol was well tolerated. Despite sevofluranes low blood:gas partition coefficient, inhalation induction was slower than i.v.-induction with propofol (67 s), although this is still clinically acceptable. Using the TCI system, with a target induction propofol concentration of 4–6 μg ml^{-1}, i.v.-induction time with propofol was not dissimilar to that previously reported (55 s).[10]

The increased incidence of involuntary movements noted in the propofol group was not significant and a trial of 134 patients in each group would be required to reach 5% statistical significance at 80% power. The use of propofol has been associated with an excitatory phenomenon.[11] Although 10% of patients induced with propofol reported pain on injection, overall induction with propofol appeared marginally smoother compared with sevoflurane. These two side effects may however discourage the choice of propofol induction, despite the relative rapidity.

Previous investigations have shown a greater decrease in MAP after induction of anaesthesia with propofol than with sevoflurane.[7 9] The effect of a bolus injection of propofol in producing a 15–30% decrease in MAP is well documented.[12] We also found a similar decrease of MAP with propofol (using TCI) and sevoflurane just before intubation, with no difference demonstrated between the groups. This can be explained largely by the fact that both agents decrease systemic vascular resistance through endothelium-mediated vasodilation,[13] which is further augmented when administered with an opioid.[12]

HR did not differ significantly between the groups during induction, but it did decrease significantly in both groups compared with baseline. Sevoflurane has been associated with slower HR,[5] and in our study TCI propofol showed a similar effect. TCI propofol has been shown to have similar haemodynamics as non-target controlled infusion.[10] The haemodynamic stability of propofol and sevoflurane during maintenance has also been demonstrated previously.[6 9] In our study the haemodynamics differed between the two groups before and after incision, whereas the HR in the sevoflurane group was considerably slower (10%) than that in the propofol group. This could be because sevoflurane has a greater effect on the resting HR. The remaining period of maintenance demonstrated generally good haemodynamic stability in both groups.

After admission to the recovery room, MAP and HR returned towards baseline levels for both groups. However, HR in the propofol group remained significantly decreased, possibly as a result of the larger administration of opioids in this group.

This study found that the number of interventions by the anaesthetist to adjust the anaesthetic depth of propofol was less than half that of sevoflurane (2.8 compared with 6 respectively). While similar amounts of morphine were used in each group, anaesthetists chose to administer more than seven times more alfentanil in the propofol group, which may have helped provide a more cardio-stable anaesthetic. Equally, patients receiving sevoflurane with nitrous oxide would require less opioid intraoperatively.

Fredman and colleagues[5] and Lien and colleagues[8] demonstrated eye opening times of between 8 and 10 min, extubation times of between 8.6 and 11 min, and times to stating names of between 11 and 15 min for both propofol and sevoflurane groups. The recovery times demonstrated in this study support these findings, despite the use of intraoperative morphine. In contrast, other investigators have found significant differences in recovery times, with sevoflurane recovery times almost half what has been reported in these studies.[7 9 15] It is possible that the addition of morphine may have masked any potential difference in recovery between sevoflurane and propofol. However, with higher intraoperative opiate administration than in previous studies [5 8] it followed that postoperative pain scores were generally very low, with the majority of patients experiencing none to mild pain at most upon regaining consciousness. A pain free recovery and faster emergence is ideal, as earlier recovery but with pain, would mean a longer stay in recovery until the patients' pain was controlled.

The recovery times after propofol administration seen here are similar to previous reports.[15] Similarly, larger standard deviations were apparent, supporting the clinical impression that a more accurate prediction of emergence times was possible following sevoflurane than following propofol.

There is strong evidence to suggest that propofol has intrinsic antiemetic properties that may persist into the postoperative period even when it is used solely as an induction agent.[16] In this study, despite the use of intraoperative opiates in both groups (with more opioid in the propofol group) nitrous oxide in the sevoflurane group and 1–3 h anaesthesia, there was a very low incidence of postoperative nausea and vomiting (PONV), with no difference between the groups. This may be because spinal surgery is associated with a low incidence of PONV.

The affordability of an anaesthetic technique may influence its usage. This study found induction and maintenance substantially cheaper with sevoflurane (£28.06) compared with propofol (£41.43) as previously reported.[17]

The use of 66% nitrous oxide does not potentiate the anaesthetic agent, its effects are additive and thereby reduce the MAC of sevoflurane by up to 60%, thus decreasing the amount required to maintain anaesthesia. It is possible that nitrous oxide has a similar effect on propofol, being attributed to decrease EC_{50} (the effective concentration at which 50% of patients do not respond to a painful stimuli) by approximately 30%.[18] Thus, adding nitrous oxide could reduce the maintenance dose of propofol, therefore decreasing cost. Maintenance with sevoflurane was based on a fresh gas flow of 3 litre min^{-1}. A much lower fresh gas flow would reduce the amount of sevoflurane used.

On approaching patients preoperatively, inhalational induction was not as popular as the use of i.v.-induction agents, but this could be attributed to previous experiences. However, postoperatively, the majority described either technique as a 'pleasant' experience, and would choose the same anaesthetic again. In this study there were only two cases (one from each group) where induction was reported as 'unpleasant'. Previous evaluations have reported the odour of sevoflurane to be pleasant and popular with almost all patients.[5 19] In contrast, it has also been reported that significantly more patients (although a minority) who have received sevoflurane have been noted to prefer a different technique in future compared with propofol.[7]

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Appendix

The total volume of propofol was as stated on the TCI unit at the conclusion of anaesthetic, and the total liquid volume of sevoflurane was calculated from the volume of vapour produced per ml of liquid (182.7 ml), fresh gas flow, per cent concentration and duration of anaesthetic.

The list prices (BNF 38; September 1999) used for this study were as follows.

Propofol: £10.67 for a 50 ml propofol prefilled syringe 1%.

Sevoflurane: £123.00 for a 250 ml bottle.

The cost of propofol was calculated using the formula

Cost (£) = (List price of propofol prefilled syringe 1% / 50)×total dose (ml)

The cost of sevoflurane was calculated using the formula

Cost (£) = ((fresh gas flow (ml)×% sevoflurane) / ml vapour per ml liquid anaesthetic (182.7))×time (min)×(price of bottle / 250)

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A series of thyroplasty cases under general anaesthesia

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Thyroplasty is an operation on the upper airway to improve voice quality in patients with unilateral vocal cord paralysis. It requires access to an uninstrumented larynx and a functional assessment of vocal cord medialization. It is a difficult anaesthetic procedure that requires sharing the airway with the surgeon. We describe an anaesthetic technique to give good operating conditions and a safe airway, using total intravenous anaesthesia, a laryngeal mask airway and intraoperative fibreoptic endoscopic assessment of the larynx, and present a series of 13 patients. Other anaesthetic techniques for thyroplasty are described and discussed.

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Type I thyroplasty is a form of medialization laryngoplasty which is used to improve laryngeal competence and voice quality in patients with unilateral adductor vocal cord paralysis. It was first described by Isshiki in 1974,[1] and has become popular since the late 1980s.[2] It involves cutting a window in the thyroid ala lateral to the vocalis muscle. A silastic implant is then placed within this window between the inner and outer perichondrium. The paralysed vocal cord is displaced medially sufficient to abut against the non-paralysed vocal cord in adduction, hence achieving laryngeal closure.

Several different anaesthetic techniques have been described for thyroplasty. These include local anaesthesia both alone[3] and combined with midazolam sedation and flumazenil reversal.[4] General anaesthesia has been used for part of the procedure.[5] Such techniques all require the patient to be awake and able to phonate to allow the surgeon to judge optimal vocal cord medialization. However, it can be difficult to perform precision surgery on the larynx in the awake patient if manipulation of the larynx leads to reflex responses such as swallowing and coughing. The technique we describe uses continuous general anaesthesia, and provides a quiet operative field. This facilitates exact surgery and allows an accurate assessment of vocal cord medialization. A single case report, employing a similar technique was published, which showed a successful outcome.[6]

Method

Between May 1997 and January 2000, 13 adult patients with unilateral adductor vocal paralysis underwent a thyroplasty operation performed by the same surgeon using the following anaesthetic technique.

Temazepam 20 mg orally, was given as pre-medication. Anaesthetic monitoring consisted of ECG, non-invasive blood pressure, pulse oximetry and capnography. A total intravenous (i.v.) anaesthetic technique used a target controlled infusion of propofol (4–10 $\mu g\ ml^{-1}$). After induction of anaesthesia, a standard laryngeal mask airway (LMA[†]) was inserted in the normal manner. A fibreoptic intubating endoscope was passed down the LMA to verify that the vocal cords were clearly visible through the distal aperture. Correct preoperative placement of the LMA is an essential requirement for thyroplasty using our technique. The breathing circuit was connected to the LMA using a catheter mount incorporating a rubber seal suction port. The patients breathed an oxygen enriched air mixture spontaneously. Small incremental i.v. doses of alfentanil were given as needed. Infiltration of the operation site with a mixture of lignocaine and epinephrine was carried out by the surgeon.

During the procedure a wide-bore flexible endoscope with an attached video camera was inserted through the suction port of the catheter mount and passed down the LMA. The resulting image of the vocal cords was displayed on a television screen. The surgeon used this image to carry out the thyroplasty and achieve optimal medialization of the paralysed vocal cord. Additional confirmation of a satisfactory airway was given by the presence of an adequate respiratory excursion of the breathing circuit reservoir bag and the display of a normal capnograph trace assessed both pre and postoperatively.

[†] LMA® is the property of Intervent Limited.

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Table 1 Patient data, measured range of parameters during thyroplasty surgery and complications observed peri and postoperatively

Patient no.	Age (yr)	Primary condition causing vocal cord palsy	Duration of procedure (min)	$F\text{I}_{O_2}$	Pulse oximetry saturation (%)	$^{ET}CO_2$ (mm Hg)	Complications
1	20	Closure of PDA	100	0.7	99	35–36	None
2	76	L Radical pnuemonectomy	110	0.6–1	93–99	52–60	Displaced LMA
3	73	L Lung squamous cell carcinoma	135	0.5	92–98	47–62	Perforation of perichondrium
4	67	Squamous oesphageal carcinoma mediastinal nodes	130	0.6	98–99	56–61	None
5	54	L+R Lung adenocarcinoma	110	0.9	95–98	52–68	Wound breakdown post-op
6	54	L Upper lobectomy clear cell carcinoma	95	0.6	98–99	36–50	None
7	51	L Lung adenocarcinoma	115	0.9	97–99	37–54	None
8	67	L Lung squamous cell carcinoma	90	0.5–0.6	99	30–61	None
9	61	Chronic fibrotic lung disease	80	0.8–0.9	97–98	50–74	None
10	69	L Lung small cell carcinoma	90	0.5	93–98	38–42	None
11	75	L Lung adenocarcinoma	145	0.5–1	97–99	40–68	Laryngeal oedema, difficult to ventilate .... epinephrine given
12	80	Thyroidectomy	120	1.0	99	35–36	None
13	57	L Upper lobectomy squamous cell carcinoma	70	0.8	97–98	44–56	None

At the conclusion of surgery the propofol infusion was discontinued and the patient transferred to the recovery room. The LMA was removed upon emergence of the patient from anaesthesia. Requirement for analgesics after operation was minimal, and simple oral paracetamol based preparations were sufficient.

Results

Patient data are summarized in Table 1. There were seven females and six males in our study, mean age 61.8 yr (range 20–80 yr). All patients had a reasonable preoperative exercise tolerance and were predicted to breathe spontaneously under general anaesthesia satisfactorily. The condition causing vocal cord palsy was metastasizing bronchial carcinoma (six patients), oesophageal carcinoma (one patient) and a chronic fibrosing lung condition (one patient). In the remaining five patients surgical trauma had caused vocal cord palsy. The youngest and fittest patient in our series had hoarseness from a patent ductus arteriosus operation in infancy.

The fractional inspired oxygen concentration during the procedure ranged from 0.5 to 1.0. All the patients breathed spontaneously. The lowest pulse oxygen saturation during the procedure was 92%. End tidal $P\text{CO}_2$ ranged from 30 to 74 mm Hg. Of the 13 thyroplasties performed in this series only one has been incomplete. Twelve patients have had good results from their thyroplasty as judged by an improvement in voice quality. Voice quality was assessed before and after surgery with a standard set of phonation exercises. An improvement in cough effort and clearance of respiratory secretions was reported but this was not assessed objectively.

There were three anaesthetic complications. The first involved partial misplacement of the LMA and caused repeated short episodes of airway obstruction associated with surgical dissection of thyroid ala.

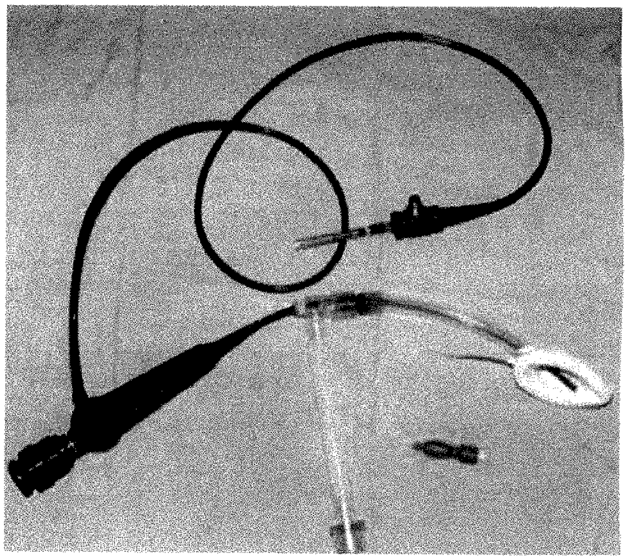

Fig 1 Fibreoptic instrumentation of the LMA used to enable visualization of the vocal cords.

When the fibreoptic endoscope was passed down the LMA the epiglottis was seen folded under the LMA and was partially obstructing the laryngeal inlet. The LMA was removed, correctly re-positioned and the thyroplasty then proceeded uneventfully. As a result of this complication we now check LMA placement in the anaesthetic room with the fibre scope and have had no further intraoperative problems with LMA placement. The second complication involved the intraoperative displacement of the silastic block perforating through the inner perichondrium and mucosa into the larynx. A small haematoma occurred but this was not associated with any clinical or endoscopic signs of airway obstruction.

The third complication occurred in the eleventh patient of our series. This case was surgically very difficult and involved numerous attempts at securing optimal vocal cord medialization. The patient became stridulous; endoscopically both vocal cords could be clearly seen becoming increasingly oedematous. On anaesthetic advice this thyroplasty was abandoned. Dexamethasone 16 mg was given i.v., and epinephrine 5 mg was nebulized in oxygen down the LMA. The stridor decreased and by the time of LMA removal, in the recovery room, had largely resolved. During this episode of laryngeal oedema the oxygen saturation on 100% oxygen remained between 97 and 99% and the end-tidal carbon dioxide ranged between 40 and 68 mm Hg.

Discussion

The surgical impetus for thyroplasty stems from the expectation that it produces better voice quality in unilateral vocal cord paralysis than the conventional para-vocal cord injection of teflon. Surgery on the shared airway is challenging for the anaesthetist. This technique provides a safe anaesthetic airway and optimal operating conditions for the surgeon.

General anaesthesia for thyroplasty facilitates precision surgery with a quiet surgical field and suppression of reflex responses, which occur during laryngeal manipulation on an awake patient. By using an LMA the larynx remains uninstrumented and yet the airway is secure. The LMA also provides a conduit for fibreoptic endoscopic assessment of vocal cord medialization. A functional assessment of airway patency at the time of the thyroplasty can also be made as the patient is breathing spontaneously. If breathing becomes inadequate positive pressure ventilation can be given via the LMA. This technique gives more airway control than to sedation techniques.[4] The assessment of optimal vocal cord medialization can occur under anaesthesia during the procedure, so that the patient does not have to wake until the end of the operation compared with previous general anaesthetic techniques.[5] With an oxygen/air mixture endoscopy is tolerated without any decrease in oxygen saturation.

Thyroplasty can cause airway obstruction by haematoma or oedema. Intraoperative stridor due to laryngeal oedema occurred in one of the above cases and responded to nebulized epinephrine and i.v. steroid. However. surgery was abandoned. We keep a cylinder containing a mixture of helium and oxygen available for the stridulous patient, but so far it has not been used. Facilities for emergency tracheostomy are mandatory during this procedure.

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Perioperative blood salvage during surgical correction of craniosynostosis in infants

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Surgical correction of craniosynostosis in infants is a very haemorrhagic procedure. The aim of this study was to determine whether the perioperative use of the continuous autotransfusion system (CATS) would reduce homologous transfusion during repair of craniosynostosis. Two groups of patients were studied according to the availability of the CATS in our hospital. The control group had surgery before the system was introduced and the study group had operations subsequently. Use of CATS was associated with a significant decrease in the median (95% confidence interval) volume of homologous blood transfused [413 (250–540) ml in the control group versus 317 (150–410) ml in the CATS group, P=0.02] and in the median (95% confidence interval) number of packed red cell units transfused [2 (1–2) in the control group versus 1 (1–2) in the CATS group, P=0.04] in the perioperative period. Use of CATS is associated with a reduction in homologous transfusion during the surgical correction of craniosynostosis in infants.

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Craniosynostosis is a relatively common disorder, related to premature closure of skull sutures, with an estimated incidence of one per 2000 live births.[1 2] Early surgical correction is mandatory, otherwise the deformation of the skull which occurs during rapid growth of the brain in infancy may lead to increased intracranial pressure in children older than 1 yr, particularly if multiple sutures are involved.[3] Surgery is aimed at restoring normal anatomy at an early age to achieve the best cosmetic result and to avoid possible cerebral consequences.[2 4] Procedures for correction of craniosynostosis are performed in young infants with a small blood volume yet represent major surgery with extensive blood loss.[5–7]

The risks associated with homologous blood transfusion (HBT) are well known.[8] They are particularly relevant in haemorrhagic surgery and have lead to the development of methods for reducing HBT,[9] including perioperative autotransfusion and blood salvaging. Perioperative autotransfusion of washed red blood cells is an established method to reduce perioperative transfusion requirements.[10] The technique was limited until recently to adults because the processing of less than 300 ml of salvaged blood was considered a contraindication to intraoperative autotransfusion;[11] the centrifugation bowls used by such devices were too large compared with the small blood volume of children. This has led to the introduction of new autotransfusion devices[12–14] with smaller bowls that can support a smaller blood volume. A new generation of autotransfusion devices (CATS, Fresenius AG, Bad Homburg, Germany), based on the technology of cell separators is also available. The CATS, introduced recently in our hospital, has a washing chamber in the shape of a double spiral, with a capacity of 30 ml, which processes shed blood continuously.[15 16]

We performed a retrospective, case-controlled study to ascertain the efficiency of perioperative autotransfusion using the CATS in infants scheduled for surgical correction of craniosynostosis. The hypothesis of this study was that the use of the CATS was associated with a reduction in the amount of homologous blood transfused.

Patients and methods

From September 1997 to April 1999, 120 surgical procedures were performed on children for the correction of a craniosynostosis in our hospital. During this period, the CATS was introduced into service and subsequently used

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Table 1 Physical characteristics and preoperative data in the control group (CONT) and in the study group (CATS). Data shown are median (95% confidence interval) or number of cases (%). There were no significant differences between the two groups

Variables	**CONT** ($n = 21$)	**CATS** ($n = 20$)
Age (months)	7 (4–11)	7.5 (6–19)
Sex ratio (M/F)	0.4	0.5
Weight (kg)	8 (7–9)	8 (7–11)
Craniosynostosis and involved sutures (n)		
Plagiocephaly: unicoronal	12 (57%)	5 (25%)
Scaphocephaly: sagittal	8 (38%)	8 (40%)
Trigonocephaly: metopic	0	1 (5%)
Brachycephaly: bicoronal	1 (5%)	6 (30%)
Haematocrit (%)	34 (33–38)	36 (34–38)
Estimated red cell volume (ml)	233 (169–286)	244 (193–326)
Number of patients with:		
Platelets count <100 000 mm^{-3}	0	0
Prothrombin time <80%	0	0
Activated partial thrombin time >42 s	0	0

routinely. Exclusion criteria for the study included the use of a postoperative closed-wound drainage autotransfusion system and incomplete data. Two groups of patients were compared. The study group (CATS) included patients who received perioperative autotransfusion using the CATS, and the control group (CONT) included the patients who did not, because they were operated on before the CATS was available.

Intraoperative management

All the procedures were performed by the same paediatric neurosurgeon under general anaesthesia without induced hypotension, after skull infiltration with epinephrine 1:200 000 in normal saline. After premedication with oral potassium clorazepate 0.5 mg kg^{-1}, general anaesthesia was induced with 8% sevoflurane and 50% nitrous oxide in oxygen, followed by sufentanil 0.5 μg kg^{-1} i.v. Neuromuscular block was achieved with vecuronium 0.1 mg kg^{-1}. After orotracheal intubation, general anaesthesia was maintained using a continuous infusion of sufentanil (0.5 μg kg^{-1} h^{-1}) and controlled ventilation with 1–1.5 MAC sevoflurane and 50% nitrous oxide in oxygen. Monitoring included continuous ECG, invasive arterial and central venous pressures (CVP), core temperature, pulse oximetry, end-tidal carbon dioxide concentration and urine output (vesical catheter) measurements. Intraoperative management was as previously described.[4 6 7] Briefly, isovolaemic compensation of blood loss was strictly observed, with fluid replacement based upon haemodynamic variables (to maintain mean arterial pressure in the range 45–55 mm Hg and CVP above 2 mm Hg) using colloid and blood transfusion. Transfusion of packed red blood cells, or of salvaged blood when available, was used to maintain an haematocrit (Hct) in the range 0.28–0.35. Fresh frozen plasma was used only in patients requiring transfusion of more than 70% of estimated blood volume.

Postoperative management

At the end of the surgical procedure, all the patients were admitted to the post-anaesthesia care unit (PACU) for ~20 h. The CATS blood saver device was used to salvage the blood during the surgical procedure and for the first 6 h in the PACU.

Measurements

Preoperative blood samples were drawn for measurement of red blood cell and platelet count (PC), haemoglobin concentration (Hb), Hct, and coagulation screening, including prothrombin time (PT) and activated partial thrombin time (aPTT). Serial blood samples were obtained for measurement of blood–gas tensions and Hct at the beginning of the surgical procedure, at least every 30 min during the operation and as frequently as clinically indicated during the perioperative stay in PACU.

For the two groups the following data were collected: the type of craniosynostosis (Table 1); physical characteristics of the patients (age and body weight at the time of surgery); preoperative clotting status (PT, aPTT, PC); and preoperative Hct (pre Hct), Hct at admission and Hct at discharge from the PACU. In addition, blood loss, the volumes of colloid and crystalloid infused, the volume of homologous and autologous blood transfused, and the number of packed red cell units used were recorded for the intraoperative period, the postoperative period and for the total duration of the study (intra- and postoperative periods).

Estimation of blood loss

In an attempt to simplify estimation of blood loss, all estimated volumes referred to red cell volumes (see Appendix). Estimated blood volume (EBV) and red cell volume (ERCV) were calculated before surgery. On the basis of a packed red blood cell Hct of 0.75 and a salvaged blood Hct of 0.65,[13] the following variables were calculated for the intraoperative, postoperative, and total period of the study: (i) estimated homologous red cell volume transfused (ERCTh); (ii) estimated autologous red cell volume transfused (ERTCa); (iii) estimated red cell transfusion (ERCT); (iv) estimated red cell deficit (ERCD); (v) estimated red cell loss (ERCL); and (vi) the percentage of the patient's ERCV lost (ERCL/ERCV).[5] All these variables (except for ERCV) were calculated for the intraoperative, postoperative and perioperative periods of the study.

Statistical analysis

The primary endpoint for assessing the efficiency of the CATS was the comparison of intraoperative, postoperative and perioperative volumes of homologous blood transfusion and the number of homologous packed red blood cell units transfused. The other variables used to ensure a comparability between the two groups were the physical characteristics and factors influencing perioperative bleeding and transfusion.

Data are expressed as mean (SD) in case of normal distribution, or as median (95% confidence interval) in case of non-normal distribution, or as number of cases (%). Statistical analysis used the unpaired Student's *t*-test in cases of normal distribution and the Mann–Whitney *U*-test in cases of non-normal distribution for continuous variables, while the Fisher's exact test was used for discrete variables. All *P* values were two-tailed, and a *P* value of less than 0.05 was required to reject the null hypothesis. Statistical analysis was performed using NCSS 6.0 software (BMDP Company, Los Angeles, CA, USA).

Results

There were 21 patients in the CONT group and 20 patients in the CATS group. All were physical ASA status I or II. There was no difference between groups with regard to physical data, the Hct in the preoperative period, Hct on admission to the PACU and discharge from the PACU, the ERCV or the clotting status (Tables 1 and 2). The volumes of crystalloid and colloid infused were not different between the two groups during the three periods studied, nor were the ERCD, ERCL and ERCL/ERCV (Tables 2 and 3).

We found a reduction in the volume of homologous blood transfused in the CATS group in the postoperative and perioperative period, but not in the intraoperative period. There was also a significant reduction in the number of packed red blood cells units transfused during the perioperative period in the CATS group (Table 4).

Discussion

The results of this study suggest that the use of the CATS autotransfusion device may significantly reduce, but is not able to avoid, homologous blood transfusion during the surgical correction of craniosynostosis in infants.

The surgical correction of craniosynostosis is usually performed in children under 6 months with a small blood volume. Relatively small blood losses can therefore have significant clinical consequences. A review of the literature shows that blood losses vary from 20% EBV to as high as 500% EBV.[17–19] The majority of studies report losses between 50 and 100% EBV.[5 6 20–22] Transfusion rates of homologous blood parallel the amount of blood loss. Thus,

Table 2 Volumes of crystalloid and colloid infused, and haematocrit (Hct) in the post-anaesthesia care unit (PACU) in the control group (CONT) and in the study group (CATS) Data shown are median (95% confidence interval) The results presented for the perioperative period are the median values (95% confidence interval) of the data obtained during the intraoperative and postoperative periods. There was no significant difference between the two groups

	Crystalloid infused (ml)	**Colloid infused (ml)**	**Hct in PACU**	
			on arrival (%)	**at discharge (%)**
Intraoperative period				
CONT group	120 (70–210)	150 (100–250)		
CATS group	140 (85–160)	190 (150–300)		
Postoperative period				
CONT group	675 (630–840)	50 (0–100)	37 (31–39)	36 (34–38)
CATS group	660 (550–800)	0 (0–100)	37 (30–41)	35 (32–37)
Perioperative period				
CONT group	960 (720–1055)	250 (180–400)		
CATS group	770 (680–940)	250 (150–350)		

Table 3 Blood loss during the three periods studied in the control group (CONT) and in the study group (CATS). Data shown are median (95% confidence interval) The results presented for the perioperative period are the median values (95% confidence interval) of the data obtained during the intraoperative and postoperative periods ERCT, estimated red cell transfused; ERCD, estimated red cell deficit; ERCV, estimated red cell volume; ERCL, estimated red cell lost, % of patient's ERCV lost, ERCL/ERCV There was no significant difference between the two groups *A negative value indicates an overcompensation of blood loss

	ERCT (ml)	**ERCD (ml)**	**ERCL (ml)**	**ERCL/ERCV (%)**
Intraoperative period				
CONT group	181 (116–287)	−1 (−10 to 11)*	176 (117–318)	84 (55–114)
CATS group	210 (112–300)	−3 (−14 to 15)*	217 (134–337)	99 (45–143)
Postoperative period				
CONT group	165 (90–187)	−3 (−12 to 9)*	159 (87–187)	78 (36–89)
CATS group	91 (59–162)	−4 (−10 to 14)*	86 (48–177)	43 (17–70)
Perioperative period				
CONT group	323 (187–405)	2 (−9 to 5)	324 (174–417)	127 (78–173)
CATS group	325 (213–478)	0 (−6 to 8)	342 (214–458)	120 (63–217)

Table 4 Comparison between the two groups regarding the volumes and number of packed red cells (PRC) transfused during the three study periods. Data are median (95% confidence interval). The results presented for the perioperative period are the median values (95% confidence interval) of the data obtained during the intraoperative and postoperative periods ***P=0.0002 versus CATS group, *P=0.02 versus CATS group, †P=0.04 versus CATS group

	Homologous transfusion (ml)	Autologous transfusion (ml)	Units of packed red cells (n)
Intraoperative period			
CONT group	242 (155–383)	0	1 (1–2)
CATS group	289 (140–400)	52 (0–145)	1 (1–2)
Postoperative period			
CONT group	150 (0–230)***	0	1 (1–2)
CATS group	0 (0–95)	112 (40–160)	1 (0–1)
Perioperative period			
CONT group	413 (250–540)*	0	2 (1–2)†
CATS group	317 (150–410)	137 (50–195)	1 (1–2)

the blood losses observed in the present study are comparable to those that we have reported previously and are also in the range reported by the majority of authors.

The introduction of CATS for blood salvage is considered a major advance in HBT reduction. This device can support, through its centrifugation bowl of 30 ml, very small volumes of blood loss. In addition, it can continuously treat blood loss, which minimizes the time required for obtaining autologous packed red cells ready for transfusion. Moreover, this device has been shown, in a recent experimental study comparing three autotransfusion devices (CATS, Haemonetics Cell Saver 5 and DIDECO Compact-A & Advanced), to be the autotransfusion device most adaptable to paediatric use.[16] In fact, continuous operation of the CATS guarantees a Hct level >60%, independent of the amount of shed blood to be processed, with a recovery rate near 100% of the processed blood.[16]

We were not able to show a reduction in HBT during the intraoperative period. This may be related to the low EBV of infants and the sudden intraoperative blood loss that cannot be salvaged by the device, due to an inevitable delay in use. The small volumes of autologous blood transfused in the intraoperative period (Table 4) support this assumption. This finding is in contrast to the results of Jimenez and Barone.[23] Surprisingly, these authors showed efficient blood salvage for the majority of their patients during the intraoperative period using the Haemonetics Cell Saver III (centrifugation bowl of 125 ml) with a relatively low blood loss.[23] However, the results of this study have been the subject of controversy.[24] On the other hand, the results of our study, regarding the efficiency of the blood salvaging technique, are in accordance with the results of others.[25 26] It should be noted that except for the study by Jimenez and Barone[23] which focused on paediatric neurosurgery, the other studies were orthopaedic, in particular scoliosis surgery.[26] In this particular type of surgery the patients are usually older and have a higher blood volume which can be more easily maintained by intraoperative autotransfusion.

The transfusion risks associated with allogenic blood are well known. Transfusion-related morbidity includes haemolysis, transfusion-related acute lung injury, bacterial contamination, post-transfusion hepatitis, graft versus host disease, haemolytic transfusion reactions, allergic reactions, leucocyte-platelet allo-immunization, acquired immunodeficiency syndrome and complications associated with massive transfusion.[8 27 28] The residual risk (per million donations) of viral transmission by seroconverting donors has been estimated to range from 1.56 for HTLV to 15.83 for HBV.[8] Serious or fatal transfusion-transmitted disease will occur in three out of 10 000 single-unit transfusions given.[29] Attempts to decrease these rates have resulted in the development of many techniques, including intraoperative blood salvage.

Our finding leads us to assume that reduction in the volume of homologous blood transfused could reduce the risk of viral transmission. However, more studies are needed to confirm such an hypothesis. There are, however, risks of perioperative blood salvage. Some reports have described complications related to the use of this device, such as transfusion of haemolysed blood,[30] acute haemolytic reactions related to inadvertently giving autologous packed red cells to the wrong patients,[31] and bacterial contamination.[32] The epidemiology of these complications is unknown: more studies on the safety of blood salving methods should be undertaken before confirming their safety.

The economic issues of blood transfusion are also of interest. Autologous blood donation has been proven to be more cost effective than homologous blood transfusion,[33] due to the relatively low price of the blood salvage kit and the potential reduction of complications related to homologous blood transfusion. But, some studies have found no cost effectiveness of intraoperative blood salvage,[26] although these have considered only the intraoperative period and the costs of long-term complications. Autotransfusion therapy may be more attractive if used both during the intraoperative and postoperative periods. In our study, autotransfusion was associated with a reduction of homologous blood transfused in the postoperative but not the intraoperative period.

Interpretation of the results must take into account the major limitations of this study, namely that it was retrospective and non-randomized. However, there was no significant difference between the two groups regarding the preoperative data (Table 1) or the factors affecting blood loss and transfusion (Tables 3 and 4). Equally, Hct in the preoperative period, on admission to the PACU and at discharge from the PACU, the clotting status, and volumes of colloid and crystalloid infused were not significantly different between the two groups. There was also no difference in blood loss between groups (Table 3). Moreover, the study was performed over a relatively short period of time (20 months) and all the patients were operated on by the same paediatric neurosurgeon, using the same surgical procedures. It is therefore unlikely that there is a methodological bias related to the study design.

In summary, we conclude that there is strong evidence for the efficiency of blood salvage in surgical correction of craniosynostosis when used intraoperatively and for the first 6 h in the PACU.

Appendix

In an attempt to simplify estimation of blood loss, all estimated volumes referred to red cell volumes.

Estimated blood volume (EBV)=80 ml kg^{-1}.

Estimated red cell volume (ERCV)=EBV × pre Hct.

Estimated homologous red cell volume transfused (ERCTh)=0.75 × volume of homologous packed red cells.

Estimated autologous red cell volume transfused (ERCTa)=0.65 × volume of autologous salvaged blood.

Estimated red cell transfused (ERCT)=ERCTh + ERCTa.

Estimated red cell deficit (ERCD)=ERCV × difference in Hct.

Estimated red cell lost (ERCL)=ERCD + ERCT.

Percentage of patient's ERCV lost=ERCL/ERCV.

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Publications on paediatric anaesthesia: a quantitative analysis of publication activity and international recognition

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A comprehensive compilation of the current international literature on paediatric anaesthesia is lacking. The aim of this study was to identify all articles on clinical practice in paediatric anaesthesia, to name the respective journals, and to assess the publication activity and international recognition of selected countries for a 6-yr period (1993–1998). The search comprised an article-to-article evaluation ('hand search') of 12 peer-reviewed anaesthesia journals, as well as an Internet-based ('SilverPlatter') Medline^{TM}-search (3.900 medical journals, US National Library of Medicine), both limited to original articles, case reports, reviews and editorials. Selected physical characteristics, for example the number of infants and children aged 0–14 yr old, the number of anaesthetists (specialists) and current impact factors (Science Citation Index) served to assess publication activity and international recognition. During the time period studied, 2259 articles (377/yr) were published on paediatric anaesthesia in 295 medical journals. The articles were primarily written in English (85.1%) and the majority originated from the USA (35.4%) and the UK (12.6%). The largest number of publications (77.7%) appeared in 29 anaesthesia journals, all referenced in Medline^{TM}, with 46% being published by only five journals. Most authors published in journals of their home country/region. Authors from the UK ranked highest in publication activity, followed by those from Canada, Switzerland, Sweden and Denmark. The highest impact factor was achieved by US and UK authors. We conclude that publications on paediatric anaesthesia are clustered in a small number of journals and are written predominantly by authors from English-speaking countries, who achieved the highest international recognition.

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Interest in paediatric anaesthesia has been growing steadily in recent years and many specialists dedicate a large share of their professional activity to this field. Special societies for paediatric anaesthesia or sections within national anaesthesia councils are involved in developing guidelines for the practice of, and continuing education in, paediatric anaesthesia. In 1997, the US-Accreditation Council for Graduate Medical Education (ACGME) acknowledged the fellowship program for paediatric anaesthesia.[1]

New medical information is communicated through international journals. The number of articles on specific topics such as paediatric anaesthesia, indicates current publication activity in the respective field. In addition to information transfer, peer-reviewed publication activity contributes to the visibility of individual authors within the medical community, and publications in highly ranked journals may promote their professional career as well as the likelihood of receiving funding from various sources.[2]

Our literature search failed to identify a quantitative evaluation of the spectrum of publications, authors and journals on paediatric anaesthesia. It was therefore the aim of this study to identify: all papers with a focus on anaesthesia in infants and children published over a 6-yr period; the respective journals; the publication activity and the international recognition achieved (according to impact factors) of the authors who were from several countries; and to characterize the publication patterns.

Methods

Data collection

The key words were selected either according to the subject (child, children, infant(s), baby, newborn, neonate(s), p(a)ediatric(s), p(a)ediatric an(a)esthesia) or to typical situations, procedures or problems, and environments in

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paediatric anaesthesia (an(a)esthesia, analgesia, an(a)esthetic(s), intubation, postoperative pain, pain therapy, postan(a)esthesia care unit, postsurgical intensive care). The search was limited to original articles, case reports, reviews and editorials. It excluded letters to the editor, historical articles, reports of meetings and abstracts. The study period was 1993–1998.

Twelve peer-reviewed serial publications in the field of anaesthesia (*Acta Anaesthesiologica Scandinavica* [1 volume/10 issues per year], *Anaesthesia* [1/12], *Anästhesiologie-Intensivmedizin-Notfallmedizin-Schmerztherapie* [1/8 in 1993–1995, 1/10 in 1996, 1/12 in 1997–1998], *Anesthesia & Analgesia* [2/12], *Anesthesiology* [2/12], *British Journal of Anaesthesia* [2/12], *Canadian Journal of Anaesthesia* [1/12], *Der Anaesthesist* [1/12], *European Journal of Anaesthesiology* [1/6], *Paediatric Anaesthesia* [1/6; 1/7 in 1997], *Pain* [4/12; 5/15 in 1996–1998], *Regional Anesthesia*, 1998 renamed *Regional Anesthesia and Pain Medicine* [1/6]) were evaluated on an article-to-article basis ('hand search'[3] [4]). The annual number of articles was determined for each journal and the abstracts were searched for the selected key words. If one of the key words was identified, the publication was registered and the first page archived. The annual subject index of every periodical was also cross-checked for all key words to ensure identification of each article on paediatric anaesthesia.

The Medline™ database was searched by PC (WinSPIRS 2.0, SilverPlatter Information, Boston, USA). Boolean operations were used (variables were the selected key words and year of publication; the above-mentioned 12 periodicals were excluded). The computerized search allowed key word identification in the title, abstract, Medical Subject Headings (MESH), and address of origin. The Medline™ report was archived for each identified contribution, including the abstract and address of the authors.

Study selection

English abstracts of all initially identified articles were assessed for clinical practice of paediatric anaesthesia. Articles related to other fields of medicine, for example surgery, cardiology, immunology or experimental research, were excluded from further evaluation. Thus, a detailed report on endoscopic findings in children anaesthetized during the procedure was excluded. In contrast, a publication describing certain paediatric anaesthesia techniques during endoscopic procedures was included.

Formal analysis

The final sample was evaluated as to language and country of origin. The origin of publications was determined according to the following algorithm: (i) address of correspondence; (ii) address of the institution; or (iii) nationality of the first author shown in previous publications by the same individual. If more than one address was indicated, the first one was used.

Physical characteristics, ranking and calculations

Numbers (1993–1998) of infants and children (aged 0–14 yr) and officially registered anaesthetists (specialists) were calculated and averaged, based on information provided by governments and national specialist societies of selected countries. The numbers of publications per 1 million children (PpmC; potential study population) and publications per 1000 anaesthetists (PptA; potential investigators) were determined by dividing the total number of relevant publications by the respective demographic factor.

It may be assumed that the number of publications together with the respective cumulative impact factor may serve to assess publication activity of a specific journal and of a country/region. Anaesthesia journals referenced in Medline™ were listed according to the number of articles on paediatric anaesthesia published during the 6-yr study period, and the respective impact factor (Science Citation Index) was averaged from 1993 to 1998.[5] The cumulative impact factor for a journal (cIF-journal) resulted from the multiplication of the number of articles therein by the respective impact factor. The cumulative impact factor for a country (cIF-country) was calculated for the seven most active countries/regions (number of articles) by adding the respective cIF-journal values of the national authors. Additionally, the mean impact factor (mIF) for the average publication on paediatric anaesthesia was obtained for each of these countries by dividing cIF-country by the number of publications for each country.

Results

We identified 2259 publications on paediatric anaesthesia in 295 peer-reviewed journals for the years 1993–1998 (377/yr). More than 58% (*n*=1325) were published in 12 anaesthesia journals, and represent 8.7% of the total number of articles published therein (*n*=15 268, 'hand searched'). A search of the Medline™ database yielded 934 articles published in 283 journals (initially 3135 in 590 journals). The articles were predominantly written in English (85.1%; Table 1) and originated in the USA or the UK (12.6% and 35.4%, respectively; Table 2).

Table 1 Language of publication

Language	*n*	%
English	1922	85.1
German	79	3.5
French	66	2.9
Other languages	192	8.5
Total	2259	100

With reference to PptA and PpmC (Table 3), authors from the UK published the largest number of articles (94.7 PptA; 28.3 PpmC), followed by those from Canada (77.4; 28.9), Switzerland (47.7; 30.3), Sweden (32.8; 27.9) and Denmark (30.9; 28.4). Considering the available manpower (anaesthetists) and the size of the potential study population (infants and children), authors from the USA (24.7; 14.0), Japan (24.1; 8.6), Germany (8.4; 10.0) and Italy (5.2; 5.6) published a relatively smaller number of articles.

Table 2 Origin of publication (according to the address of correspondence)

Country	*n*	%
USA	800	35.4
United Kingdom	284	12.6
Canada	173	7.7
Japan	169	7.5
Scandinavia	144	6.4
Germany	123	5.4
France	121	5.4
Australia	46	2.0
Other European countries	224	9.9
Other countries, worldwide	175	7.7
Total	2259	100

The annual number of publications on paediatric anaesthesia in the 12 hand-searched periodicals increased by 23.7% (from 194 to 240) from 1993 to 1998 (Table 4). For some journals, for example *Anesthesia & Analgesia* and *Paediatric Anaesthesia*, the increase was significantly greater (+80%: from 25 to 45; and +54%: from 61 to 94, respectively), whereas in others, for example *Canadian Journal of Anaesthesia* and *Masui* (Japan), there was a decrease over the same period (–86%: from 26 to 14; and –79%: from 28 to 6, respectively).

A total of 77.7% of all publications appeared in 29 anaesthesia journals listed in Medline™ (Table 5). Others were found in journals for various medical disciplines, for example surgery, intensive care medicine, emergency medicine, hygiene. Most articles (*n*=1350; 59.8%) were published in 15 serial anaesthesia journals from four English-speaking countries, that is USA (9), UK (4),

Table 3 Demographic data and analysis of publication activity on paediatric anaesthesia for selected countries
[1]US Department of Commerce, Economics and Statistics, Bureau of the Census, Washington DC, USA. [2]Office for National Statistics, London, UK. [3]Statistics Canada, Ottawa, Ontario, Canada. [4]Foreign Press Center, Tokyo, Japan. [5]Statistisches Bundesamt, Wiesbaden, Germany [6]Institute Nationale de Statistique et des Études Economiques, Paris, France. [7]Istituto nazionale di statistica, Rome, Italy [8]Australian Bureau of Statistics, Belconnen, Australia. [9]Statistiska centralbyrån-Statistics Sweden, Stockholm, Sweden. [10]Bundesamt für Statistik, Sektion Information, Bern, Switzerland [11]Central Bureau for Statistics, Den Haag, Denmark. [12]Centraal Bureau voor de Statistiek, Voorburg, The Netherlands. [13]Österreichisches Statistisches Zentralamt, Wien, Austria. [14]Best possible estimate by the Japanese Medical Society, Sapporo Local Area Medical Network. *Listed according to the number of publications on paediatric anaesthesia during 1993–1998 (*n*=1910, other countries=349). #Number of infants and children (0–14-yr-old, mean value for 1993–1998). $Anaesthetists ('specialists'), mean value for 1993–1998. CpA, children per anaesthetist, PptA, publications per thousand anaesthetists, PpmC, publications per million children

Country*	Children#	Anaesthetists $	CpA	Publications from 1993–1998		
				n	PptA	PpmC
USA	57 276 000[1]	32 344	1771	800	24.7	14.0
United Kingdom	10 033 594[2]	3000	3345	284	94.7	28.3
Canada	5 996 200[3]	2236	2682	173	77.4	28.9
Japan	19 540 000[4]	7000[14]	2791	169	24.1	8.6
Germany	12 290 775[5]	14 633	840	123	8.4	10.0
France	11 466 000[6]	7960	1440	121	15.2	10.6
Italy	8 382 507[7]	9070	924	47	5.2	5.6
Australia	3 700 000[8]	1697	2180	46	27.1	12.4
Sweden	1 649 092[9]	1401	1177	46	32.8	27.9
Switzerland	1 154 000[10]	734	1572	35	47.7	30.3
Denmark	952 188[11]	873	1091	27	30.9	28.4
Netherlands	3 787 400[12]	900	4208	20	22.2	5.3
Austria	1 392 621[13]	1227	1135	19	15.5	13.6

Table 4 Number of annual publications on paediatric anaesthesia in 12 'hand-searched' journals
PA, *Paediatric Anaesthesia*, A&A, *Anesthesia & Analgesia*, CJA, *Canadian Journal of Anaesthesia*, BJA, *British Journal of Anaesthesia*, ANSLY, *Anesthesiology*; ANSIA, *Anaesthesia*; AAS, *Acta Anaesthesiologica Scandinavica*; D-ANAE, *Der Anaesthesist*; AINS, *Anaesthesiologie-Intensivmedizin-Notfallmedizin-Schmerztherapie*, EJA, *European Journal of Anaesthesiology*; RA, *Regional Anesthesia*.

Year	PA	A&A	CJA	BJA	ANSLY	ANSIA	AAS	Pain	D-ANAE	AINS	EJA	RA	Total
1993	61	25	26	23	16	15	12	8	6	1	1	0	194
1994	65	20	39	26	25	14	5	6	6	6	1	3	216
1995	56	23	33	16	23	21	8	6	6	4	3	1	200
1996	73	32	35	24	24	17	10	10	5	6	5	3	244
1997	79	45	25	19	15	12	13	7	2	5	4	5	231
1998	94	45	14	22	19	11	10	3	13	1	6	2	240
Total	428	190	172	130	122	90	58	40	38	23	20	14	1325

Table 5 Publications on paediatric anaesthesia in 29 anaesthesia journals listed in Medline™

For each journal the total number of publications on paediatric anaesthesia (*n*, [1993–1998]), the respective percentage of all identified publications (%), the mean impact factor (1993–1998, ranking), as well as the respective cIF-journal (ranking) are listed. *Listed by the number of publications on paediatric anaesthesia during 1993–1998. # No impact factor available, journal not listed in 'Science Citation Index' (ISI)[5] ‡Until 1996 published as '*Regional Anesthesia*'. +No impact factor listed for the years 1993–1995. §No impact factor listed for the years 1993–1994. IF, impact factor, cIF-journal, cumulative impact factor for a journal (={[*n*] multiplied by [IF]}), F, France; UK, United Kingdom; G, Germany, NA, not available.

Anaesthesia journals listed in Medline™*	***n***	**% (*n*=2259)**	**IF [mean 1993–1998] (Rank)**	**cIF-journal [*n* × IF] (Rank)**
Paediatric Anaesthesia (UK)	428	18.94	+0.813 (13)	347.97 (03)
Anesthesia & Analgesia (USA)	190	8.41	2.471 (04)	469.49 (02)
Canadian Journal of Anaesthesia (Canada)	172	7.61	1.302 (08)	223.94 (05)
British Journal of Anaesthesia (UK)	130	5.75	2.243 (05)	291.59 (04)
Anesthesiology (USA)	121	5.35	4.622 (01)	559.26 (01)
Masui (Japan)	92	4.07	NA #	NA #
Anaesthesia (UK)	90	3.98	1.807 (06)	162.63 (06)
Journal of Clinical Anesthesia (USA)	69	3.05	§0.855 (12)	59.00 (10)
Acta Anaesthesiologica Scandinavica (Denmark)	58	2.56	1.045 (10)	60.61 (09)
Pain (The Netherlands)	40	1.77	3.730 (03)	149.20 (07)
Der Anaesthesist (G)	38	1.68	0.678 (16)	25.77 (11)
Cahiers d'Anésthesiologie (F)	35	1.55	NA #	NA #
Critical Care Medicine (USA)	34	1.51	3.848 (02)	130.83 (08)
Journal of Cardiothoracic and Vascular Anesthesia (USA)	32	1.42	0.720 (14)	23.04 (12)
Anesteziologiia i Reanimatologiia (Russia)	28	1.23	NA #	NA #
Revista Espanola de Anestesiologia y Reanimacion (Spain)	25	1.11	NA #	NA #
Anaesthesia and Intensive Care (Australia)	23	1.02	0.941 (11)	21.64 (13)
Anaesthesiologie-Intensivmedizin-Notfallmedizin-Schmerztherapie (G)	22	0.97	0.690 (15)	15.18 (15)
Minerva Anestesiologica (Italy)	22	0.97	NA #	NA #
European Journal of Anaesthesiology (UK)	20	0.89	0.623 (17)	12.46 (16)
Annales Françaises d'Anésthesie et de Réanimation (F)	17	0.75	0.317 (18)	5.39 (18)
International Anesthesiology Clinics (USA)	15	0.66	0.265 (19)	3.98 (19)
Regional Anesthesia and Pain Medicine (USA)‡	15	0.66	1.287 (09)	19.31 (14)
Acta Anaesthesiologica Sinica (Taiwan)	12	0.53	NA #	NA #
Anasthesiologie und Reanimation (G)	9	0.40	NA #	NA #
Acta Anaesthesiologica Belgica (Belgium)	6	0.27	NA #	NA #
Journal of Neurosurgical Anesthesiology (USA)	6	0.27	1.342 (07)	8.06 (17)
Anesthesia Progress (USA)	5	0.22	NA #	NA #
Klinische Anasthesiologie und Intensivtherapie (G)	1	0.04	NA #	NA #
Total	1755	77.64	29.599	2579.98

Australia (1) and Canada (1), and ~ 46% (*n*=1041) in a total of five journals (*Paediatric Anaesthesia, Anesthesia & Analgesia, Canadian Journal of Anaesthesia, British Journal of Anaesthesia* and *Anesthesiology*). One-fifth of the articles (*n*=428; 18.9%) were published in the journal *Paediatric Anaesthesia.* The difference in the impact factor of the cited journals resulted in a different ranking of the cIF-journal. For example, the cIF-journal of some periodicals was high despite the relatively smaller number of publications during the study period (e.g. *Anesthesiology*, cIF-journal=559.26; *n*=121), compared with that of journals publishing a greater number of articles (e.g. *Paediatric Anaesthesia*, cIF-journal=347.97; *n*=428).

Most authors have published their work in anaesthesia journals of their respective country or region (Table 6). Similarly, the majority of periodicals was dominated by national authors, for example 64.9% of the articles in US journals were of US origin (*n*=336). This was found even more frequently in journals from non-English-speaking countries, for example Japan, France or Germany. However, British and Canadian periodicals, for example *Paediatric Anaesthesia, Canadian Journal of Anaesthesia,* showed a greater diversity in authorship. More international representation in authorship was identified for journals published in English.

The cIF-country (Table 6) was higher for publications by US authors (1084.41), followed by the work of British (353.38) and Canadian groups (297.04). Accordingly, the calculated mIF-country was high for North American and British authors. However, publications from Scandinavia also achieved a high mIF-country (Table 7).

Discussion

General findings

There was a mean of 377 publications published each year on paediatric anaesthesia and most of the papers were written in English. The largest number of articles appeared in *Paediatric Anaesthesia, Anesthesia & Analgesia,* the *Canadian Journal of Anaesthesia,* the *British Journal of Anaesthesia* and *Anesthesiology.* British authors published most articles on the topic in relation to selected physical characteristics (e.g. age of the children and infants). Most

Table 6 Publications on paediatric anaesthesia from the seven most active countries (see Table 2) in 29 anaesthesia journals listed in Medline™ (see Table 5)

*Listed by the number of publications on paediatric anaesthesia during 1993–1998 [journals with no impact factor ('Science Citation Index', SCI^5) are not included in this table]. *n*, number of publications on paediatric anaesthesia, IF, impact factor, cIF-j, cumulative impact factor for a journal (={[*n*] multiplied by [IF]}), cIF-country, cumulative impact factor for a country (={addition of all individual [cIF-j] for each country}), F, France, UK, United Kingdom, G, Germany, Scand., Scandinavia.

Anaesthesia journals listed in Medline™ *	Number of publications (*n*) and their cumulative impact (cIF-j) from													
	USA		UK		Japan		Canada		Scandinavia		France		Germany	
	n	(cIF-j)	*n*	(cIF-j)	*n*	(cIF-j)	*n*	(cIF-j)	*n*	(cIF-j)	*n*	(cIF-j)	*n*	(cIF-j)
Paediatric Anaesthesia (UK)	118	(95.34)	118	(95.34)	20	(16.26)	21	(17.07)	36	(29.27)	20	(16.26)	15	(12.20)
Anesthesia & Analgesia (USA)	129	(318.76)	1	(2.47)	12	(29.65)	11	(27.18)	6	(14.82)	12	(29.65)	3	(7.41)
Canadian Journal of Anaesthesia (Canada)	43	(55.99)	3	(3.91)	16	(20.83)	85	(110.67)	1	(1.30)	7	(9.11)	0	—
British Journal of Anaesthesia (UK)	3	(6.72)	60	(134.58)	6	(13.46)	1	(2.24)	17	(38.13)	11	(24.67)	6	(13.46)
Anesthesiology (USA)	77	(355.89)	1	(4.62)	14	(64.71)	13	(60.09)	3	(13.87)	4	(18.49)	2	(9.24)
Anaesthesia (UK)	2	(3.61)	53	(95.77)	2	(3.61)	2	(3.61)	7	(12.65)	1	(1.81)	0	—
Journal of Clinical Anesthesia (USA)	59	(50.45)	0	—	0	—	1	(0.86)	2	(1.71)	1	(0.86)	1	(0.86)
Acta Anaesthesiologica Scandinavica (Denmark)	0	—	2	(2.09)	2	(2.09)	0	—	36	(37.62)	3	(3.14)	3	(3.14)
Pain (The Netherlands)	13	(48.49)	2	(7.46)	0	—	20	(74.60)	2	(7.46)	1	(3.73)	0	—
Der Anaesthesist (G)	0	—	0	—	0	—	0	—	0	—	0	—	33	(22.37)
Critical Care Medicine (USA)	31	(119.29)	0	—	0	—	0	—	0	—	1	(3.85)	0	—
Journal of Cardiothoracic and Vascular Anesthesia (USA)	18	(12.96)	3	(2.16)	0	—	1	(0.72)	3	(2.16)	2	(1.44)	2	(1.44)
Anaesthesia and Intensive Care (Australia)	0	—	1	(0.94)	1	(0.94)	0	—	0	—	0	—	0	—
Anaesthesiologie-Intensivmedizin-Notfallmedizin-Schmerztherapie (G)	1	(0.69)	0	—	0	—	0	—	0	—	0	—	20	(13.80)
European Journal of Anaesthesiology (UK)	0	—	4	(2.49)	0	—	0	—	4	(2.49)	1	(0.62)	5	(3.12)
Annales Françaises d'Anésthesie et de Réanimation (F)	0	—	0	—	0	—	0	—	1	(0.32)	14	(4.44)	0	—
International Anesthesiology Clinics (USA)	12	(3.18)	1	(0.26)	0	—	0	—	0	—	1	(0.26)	0	—
Journal of Neurosurgical Anesthesiology (USA)	3	(4.03)	0	—	1	(1.34)	0	—	0	—	0	—	1	(1.34)
Regional Anesthesia and Pain Medicine (USA)	7	(9.01)	1	(1.29)	1	(1.29)	0	—	0	—	1	(1.29)	0	—
Total (cIF-country)	518	(1084.41)	250	(353.38)	167	(152.89)	155	(297.04)	119	(161.80)	105	(119.62)	101	(88.38)

Table 7 Mean impact factor of publications on paediatric anaesthesia
*Listed by the number of publications on paediatric anaesthesia from 1993 to 1998 (see Table 5) §mIF={[cumulative IF-country, see Table 6] divided by [all publications in anaesthesia journals of the same country, (including articles in those journals, for which no impact factor was available; see Table 5)]}

Country*	MIF§
USA	2 122
United Kingdom	1.414
Japan	0 916
Canada	1.916
Scandinavia	1 360
France	1.139
Germany	0 875

work originated from the USA and the UK. These articles were also published in the journals with the highest impact factors in the field, resulting in high international recognition.

Limitations and advantages of the applied method

The limitations of this exercise were that Medline™ (US National Library of Medicine, 1999) only references 3900 of ~165 000 published journals worldwide.[6] Furthermore, we excluded book chapters, abstracts, popular science publications or rejected manuscripts, all of which reflect publication activity. The advantages of this restrictive approach were that all included articles underwent peer-review ensuring a specific level of quality, and that subjective or random factors such as accessibility were eliminated making the results reproducible. Furthermore, because only work on 'clinical' paediatric anaesthesia was included in our study, some publications with potentially relevant information may not have been identified.

The selection of key words and the criteria for inclusion or exclusion of the retrieved articles was dependent upon the decision of the investigators. Other search terms or selection criteria might have yielded different data. In addition, as the correspondence address listed may not always have represented the country of origin of all the authors involved, we were unable to quantify foreign contributions to specific papers.

Journals

Approximately 78% of all publications appeared in anaesthesia journals, and 46% of the articles were found in five periodicals (*Paediatric Anaesthesia, Anesthesia & Analgesia, Canadian Journal of Anaesthesia, British Journal of Anaesthesia* and *Anesthesiology*). While these journals may be of vital interest to paediatric anaesthetists worldwide, other anaesthesia journals may also be important, because for instance they reflect activities in the country of the respective reader.

Increases in the number of articles on paediatric anaesthesia (24%) were smaller than increases in publications on medical topics as a whole (33%).[6] Larger or smaller increases in some journals may be a reflection of editorial board decisions. For example, *Anesthesia & Analgesia* became the official journal of the 'American Society of Pediatric Anesthesia' in 1996,[1] and the number of publications on paediatric anaesthesia increased accordingly. This may have led to fewer publications elsewhere, for instance in the *Canadian Journal of Anaesthesia* or in *Masui.* Alternatively, the impact factor of a journal (e.g. *Anesthesia & Analgesia*, IF=2.471; Table 5) could play an important role in manuscript submission. Some authors, for instance from Japan, may have preferred to submit their manuscripts there, which in turn, resulted in fewer submissions to Japanese journals.

Paediatric Anaesthesia has an important position with ~19% of all publications in the field, although the impact factor (0.813) is ranked relatively low. The relevance of the impact factor to estimate importance and quality of scientific output has become the subject of intense debate.[7–15] It has been suggested that the impact factor reflects international recognition or 'visibility', rather than the quality or importance of certain periodicals or a researcher's work.[16] Some journals may have an important role independent of their impact factor as they convey specific information for interested specialists.

Publication productivity and international recognition of different countries/regions

The largest proportion of publications on paediatric anaesthesia originated from the USA and the UK, which is in proportion to medical research output in general.[6] American and British authors may publish more frequently, due to special mechanisms of fund-raising and career development in their home countries. The high productivity of anaesthetists from the UK and several smaller European countries, Switzerland, Sweden, Denmark, was to be expected as it is similar to the publication pattern in other medical areas.[4 17–19] Differences in publication productivity between countries have been associated with differences in the respective medical systems and other factors such as language, training and funding.[17]

Alternatively, work from highly productive countries may have been published preferentially. A strong correlation between the origins of medical journals and the respective authors has previously been observed in related fields, for example anaesthesia, intensive care, emergency medicine and pain management.[14 18 19] Apart from the scientific content, which is evaluated through a vigorous peer-review process, it has been suggested that acceptance of manuscripts may be influenced by various co-factors. For example, the probability of having an English language manuscript accepted is greater than the acceptance of a non-English version.[20] Furthermore, the majority of authors publishing in highly ranked USA- or UK-based journals write in their native language, originate from countries with a high scientific reputation, and their reviewers may be from the same country. Thus, it has been suggested that work by Anglo-American authors is more likely to be accepted by Anglo-American journals, resulting in a certain publication bias.[21–24]

Some of these factors may exert an additional influence on publication patterns in paediatric anaesthesia. However, our data appear to support the view that anaesthetists from certain countries, in relation to the respective available manpower and/or study population, are more active in communicating new information on paediatric anaesthesia to the scientific community. Together with the higher impact factors of the journals, this results in higher cumulative and mean impact factors for both North American and British publications, and thus in greater international recognition or 'visibility' (i.e. number of publications multiplied by the impact factor).[16] The high cumulative and mean impact factors of some European countries/regions, may additionally result from the lack of non-English language anaesthesia journals in these countries, leading the authors to publish elsewhere.

In conclusion, *Paediatric Anaesthesia*, *Anesthesia & Analgesia*, the *Canadian Journal of Anaesthesia*, the *British Journal of Anaesthesia* and *Anesthesiology* are important journals for the paediatric anaesthetist, as they account for ~46% of all publications in this field. Publications on paediatric anaesthesia with the greatest international recognition (according to the impact factor) originated from the US and the UK. This may be due to a high publication productivity of authors from the respective countries, and certain co-factors supporting publication in the highly ranked USA- and UK-based periodicals. The 'lingua franca' of scientific publications is English, a factor that cannot be ignored by non-native speakers of English who wish to influence paediatric anaesthesia.

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Gastric mucosal end-tidal $P\text{CO}_2$ difference as a continuous indicator of splanchnic perfusion

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Gastric mucosal and arterial blood $P\text{CO}_2$ must be known to assess mucosal perfusion by means of gastric tonometry. As end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) is a function of arterial $P\text{CO}_2$, the gradient between $P\text{E}'_{\text{CO}_2}$ and gastric mucosal $P\text{CO}_2$ may reflect mucosal perfusion. We studied the agreement between two methods to monitor gut perfusion. We measured the difference between gastric mucosal $P\text{CO}_2$ (air tonometry) and $P\text{E}'_{\text{CO}_2}$ (=$\text{D}P\text{CO}_{2\text{gas}}$) and the difference between gastric mucosal $P\text{CO}_2$ (saline tonometry) and arterial blood $P\text{CO}_2$ (=$\text{D}P\text{CO}_{2\text{sal}}$) in 20 patients with or without lung injury. $\text{D}P\text{CO}_{2\text{gas}}$ was greater than $\text{D}P\text{CO}_{2\text{sal}}$ but changes in $\text{D}P\text{CO}_{2\text{gas}}$ reflected changes in $\text{D}P\text{CO}_{2\text{sal}}$. The bias between $\text{D}P\text{CO}_{2\text{gas}}$ and $\text{D}P\text{CO}_{2\text{sal}}$ was 0.85 kPa and precision 1.25 kPa. The disagreement between $\text{D}P\text{CO}_{2\text{gas}}$ and $\text{D}P\text{CO}_{2\text{sal}}$ increased with increasing dead space. We propose that the disagreement between the two methods studied may not be clinically important and that $\text{D}P\text{CO}_{2\text{gas}}$ may be a method for continuous estimation of splanchnic perfusion.

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Gastrointestinal hypoperfusion may lead to organ dysfunction, increased mortality and increased cost of care of critically ill patients.[1–3] However, we do not have a practical method for assessment of gut mucosal perfusion.[4–6] Gastrointestinal saline tonometry is still controversial and not routinely used in critical care, for several reasons. Originally the gastric tonometer was designed to measure gastric mucosal $P\text{CO}_2$ which was then used to calculate gastric mucosal pH (pH_i).[7 8] Gastric mucosal pH was assumed to reflect splanchnic perfusion and oxygenation. However, the calculation of pH_i necessitates both taking arterial blood sample to measure bicarbonate concentration and the use of a cumbersome formula. In addition, experimental and clinical studies have shown that the calculation of pH_i using arterial blood bicarbonate concentration may be incorrect, the use of pH_i alone ignores the effects of systemic acid–base status on gastric mucosal pH and there is also a potential bias from the measurement of saline $P\text{CO}_2$ with different blood gas analysers.[9–11]

The measurement of gastric mucosal $P\text{CO}_2$ has become more popular in experimental and clinical studies and avoids the potential problems of pH_i. An automated gas tonometer was developed to measure gastric mucosal $P\text{CO}_2$, so that repeated analysis of saline samples for $P\text{CO}_2$ and the potential errors of analysis are eliminated and the measurements are now easier.[10 12 13] Clinical and experimental studies have validated gas tonometry using conventional saline tonometry as a reference.[14–16] However, the gradient between systemic $P\text{CO}_2$ and gastric mucosal $P\text{CO}_2$ is the variable of interest that reflects mucosal perfusion.[4 17] Repeated arterial blood samples are needed to measure blood $P\text{CO}_2$ which may not be feasible in clinical practice and may make clinicians unwilling to use gastric tonometry. On the other hand, without continuous or semi-continuous measurements important episodes of splanchnic hypoperfusion may not be noticed.

The partial pressure of carbon dioxide (CO_2) of end expiratory gas (end tidal CO_2, $P\text{E}'_{\text{CO}_2}$) can be used to estimate arterial $P\text{CO}_2$.[18] $P\text{E}'_{\text{CO}_2}$ is routinely monitored in intubated patients although $P\text{E}'_{\text{CO}_2}$ does not necessarily accurately represent arterial CO_2 if the proportion of dead space ventilation is increased as in patients with lung

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injury.[19] However, the difference between $P\mathrm{E}'_{\mathrm{CO}_2}$ and gastric mucosal CO_2 (measured by gas tonometry) could reflect gastric mucosal perfusion continuously or semi-continuously without a need for laboratory testing. We hypothesized that this would be the case even in patients with increased physiologic dead space, providing that the dead space remains relatively constant. To our knowledge this possibility has not been tested. We designed our study to investigate if the gradient between gastric mucosal $P\mathrm{CO}_2$ and end-tidal CO_2 can be used to monitor gastric mucosal perfusion.

Patients and methods

The study was approved by the Ethics Committee of the Kuopio University Hospital and a written informed consent was obtained either from the patient (patients recovering from cardiac surgery), or from the relatives (patients with acute lung injury, ALI). We studied 10 patients who were recovering from cardiac surgery (and who did not have lung injury) and 10 patients who had ALI. We defined ALI as $Pa_{\mathrm{O}_2}/FI_{\mathrm{O}_2}$ less than 200 mm Hg (26.7 kPa). We studied patients with ALI because increased dead space ventilation increases the difference between arterial CO_2 and $P\mathrm{E}'_{\mathrm{CO}_2}$ and this may reduce the accuracy of gastric-mucosal end-tidal $P\mathrm{CO}_2$ difference to indicate gastric-mucosal arterial $P\mathrm{CO}_2$ difference (gastric-mucosal end-tidal $P\mathrm{CO}_2$ tends to be higher than gastric-mucosal arterial $P\mathrm{CO}_2$ difference). All patients were intubated, mechanically ventilated (Servo 900C, Siemens AB, Solna, Sweden) and sedated as clinically appropriate during the measurements.

Two gastric tonometers, a gas and a saline tonometer, were inserted in each patient via mouth. The correct positions of the tips of the tonometers were confirmed by x-ray. We used continuous gastric suctioning but H_2-blockers were not given to any patient.[20 21] Gas tonometer (Tonocap®, Datex/Instrumentarium, Helsinki, Finland) was used to measure gastric mucosal partial pressure of carbon dioxide (Pr_{CO_2}) in 15 min intervals during the 8 h study period. In Tonocap® the device fills the tonometer TRIP-catheter (Tonometrics, Datex/Instrumentarium, Finland) with 5 ml gas (air) and a sample of this gas is drawn after an equilibration period. The $P\mathrm{CO}_2$ of this sample is measured by Tonocap® using the same standard infra-red method that is used to measure the partial pressure of end-tidal CO_2 ($P\mathrm{E}'_{\mathrm{CO}_2}$). A time dependent correction factor of 1.12 (for incomplete equilibration time of 15 min) for the mucosal $P\mathrm{CO}_2$ (Pr_{CO_2}) was used. The Tonocap® was calibrated before the measurements according to the manufacturer's recommendation using calibration gas (5±0.03% CO_2 in 95% oxygen, Datex/Instrumentarium, Helsinki, Finland). The mean value of Pr_{CO_2} was calculated each hour to allow comparison between gas and saline tonometers. End-tidal CO_2 was measured from the expired air immediately distal to the intubation tube using an AS3 monitor (Datex/Instrumentarium, Helsinki, Finland). The gastric-mucosal end-tidal $P\mathrm{CO}_2$ difference ($\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$) was calculated by subtracting end tidal $P\mathrm{CO}_2$ from gastric mucosal $P\mathrm{CO}_2$ (as measured by Tonocap®).

We measured Pr_{CO_2} using conventional saline tonometry and arterial $P\mathrm{CO}_2$ each hour throughout the study. With the saline tonometry Pr_{CO_2} was measured using 2.5 ml of sodium chloride in the tonometer balloon. Both the saline and arterial blood samples were analysed within 2 min of withdrawal using a blood–gas analyser (ABL-520, Radiometer, Copenhagen, Denmark). We did not take into account the potential bias related to blood gas analyser.[10] A time dependent correction factor of 1.13 (for incomplete equilibration time of 60 min) for the Pr_{CO_2} was used with saline tonometry and the measurements were carried out according to the manufacturer's recommendations. Gastric-mucosal arterial $P\mathrm{CO}_2$ difference ($\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$) was calculated by subtracting arterial $P\mathrm{CO}_2$ from gastric mucosal $P\mathrm{CO}_2$ (as measured by saline tonometry). We regarded this difference ($\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$) as the reference to represent true systemic-gastric mucosal $P\mathrm{CO}_2$. In addition to the comparison between $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$ and $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$, we also compared the differences between gastric mucosal $P\mathrm{CO}_2$ (measured using gas tonometry) and arterial blood $P\mathrm{CO}_2$ or end-tidal $P\mathrm{CO}_2$. This was done to eliminate potential errors in the saline technique, such as those related to blood–gas analyser bias, inappropriate equilibration factors and tonometer catheter dead space effects.

Arterial end-tidal $P\mathrm{CO}_2$ difference was calculated by subtracting end-tidal $P\mathrm{CO}_2$ from arterial blood $P\mathrm{CO}_2$. This gradient was calculated to indirectly estimate dead space ventilation of the lung. The higher the gradient between arterial (Pa_{CO_2}) end-tidal $P\mathrm{CO}_2$ ($P\mathrm{E}'_{\mathrm{CO}_2}$), the higher is the dead space ventilation of the lung. The fraction (%) of dead space ventilation ($V\mathrm{D}/V\mathrm{T}$) was estimated using the following equation: $V\mathrm{D}/V\mathrm{T} = (Pa_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2})/Pa_{\mathrm{CO}_2}$.

Statistical analysis

Our main interest in the analysis was to study the agreement between $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ and $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$. We studied this agreement using the method described by Bland and Altman.[22] In addition to graphical display we also calculated bias (the mean difference between the two measurements) and precision (SD of the bias) for this comparison. Because we repeated measurements, the effect of time, and particularly time by group ($\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ or $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$) interaction, was analysed using general linear model with repeated measures option (statistical package SPSS for Windows, version 7.5). This analysis was carried out to test whether changes in gastric-mucosal systemic $P\mathrm{CO}_2$ difference during the study were similar for $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ and $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$. We used regression analysis to study the correlation between two variables and *t*-test when appropriate. A *P*-value of <0.05 was considered statistically significant. Results are given as mean (SD).

Results

The fraction of dead space ventilation was 11 (7)% (mean (SD)) in CABG patients and 25 (12)% in patients with ALI ($P<0.001$). The mean values and standard deviations of gastric mucosal end tidal $P\mathrm{CO_2}$ difference ($\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$) and gastric mucosal arterial $P\mathrm{CO_2}$ difference ($\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$) for each hour during the whole study period are shown in Figure 1. When all patients were analysed together there was a significant effect of time ($P<0.01$) but no time by group interaction ($P=0.33$) indicating that the changes of gastric mucosal-systemic $P\mathrm{CO_2}$ difference were similar for $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$ and $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$. Also in this analysis the group effect was not significant ($P=0.084$). $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ tended to be greater that $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$ both in patients with ALI and in patients recovering from cardiac surgery. However, the difference between the two methods was greater in patients with ALI. Figure 2 shows that the agreement between the two methods to reflect gastric mucosal systemic $P\mathrm{CO_2}$ is reasonably good, except for higher mean gastric mucosal systemic $P\mathrm{CO_2}$ differences. With greater mean gastric mucosal-systemic $P\mathrm{CO_2}$ differences, $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ tends to overestimate $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$ (Fig. 2). The bias and the precision of this comparison are 0.85 and 1.25 kPa, respectively. The comparison between gastric mucosal $P\mathrm{CO_2}$ (measured by gas tonometry) and arterial blood $P\mathrm{CO_2}$ or end-tidal $\mathrm{CO_2}$ is shown in Figure 3. The difference between gastric mucosal $P\mathrm{CO_2}$ (gas tonometry) and end-tidal $\mathrm{CO_2}$ was higher ($P=0.022$, 'group' effect) than the difference between gastric mucosal $P\mathrm{CO_2}$ (gas tonometry) and arterial blood $P\mathrm{CO_2}$. In addition, the effect of time was significant ($P<0.001$) but there was no time by group interaction ($P=0.9$). In Bland and Altman analysis the bias and the precision of this comparison are 1.08 and 0.85 kPa, respectively (figure not shown).

As expected, the difference between $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ and $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$ increased with increasing arterial end-tidal $P\mathrm{CO_2}$ difference (Fig. 4). Figure 5 shows a reasonable correlation between the maximum change from baseline in $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$ and the corresponding change in $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$. The correlation in gastric mucosal $P\mathrm{CO_2}$, when it was measured both by saline and by gas tonometry, is shown in Figure 6 and the Bland–Altman plot for the same comparison in Figure 7. The bias in this Bland–Altman analysis was –0.26 kPa and the precision 0.81 kPa. Finally, the correlation showing the mean gastric mucosal $P\mathrm{CO_2}$ (measured by air and saline tonometry) for each patient during the whole study period is shown in Figure 8.

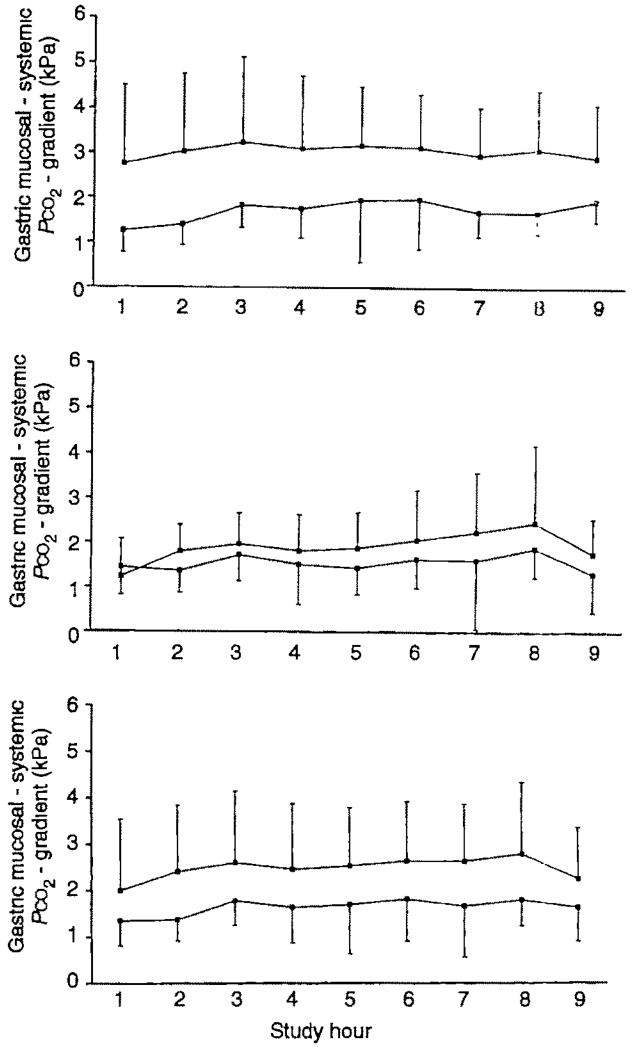

Fig 1 Gastric mucosal end tidal $P\mathrm{CO_2}$ difference ($\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$) and gastric mucosal-arterial $P\mathrm{CO_2}$ difference ($\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$) (mean (SD)) during the 8 h study period. (Top) Patients with ALI; (middle) patients recovering from cardiac surgery; (bottom) all patients combined. When all patients were analysed together (bottom) using general linear model there was a significant effect of time ($P<0.01$) but no time by group ($\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ or $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$) interaction ($P=0.33$)

Discussion

We found that the difference between gastric mucosal $P\mathrm{CO_2}$ (measured by gas tonometry) and end-tidal $P\mathrm{CO_2}$ ($\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$) reflects the difference between gastric mucosal $P\mathrm{CO_2}$ (measured by saline tonometry) and arterial $P\mathrm{CO_2}$ ($\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$). We also found that $P\mathrm{CO}_{2\mathrm{gas}}$ systematically overestimated $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$ and that $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ has some obvious limitations. However, the agreement between the two methods is acceptable and allows $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ to be used in clinical practice as a semi-continous indicator of the adequacy of splanchnic perfusion.

The advantage of $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ is that it reflects the adequacy of gastric mucosal perfusion continuously. A monitor is a warning device that reveals progressive change, e.g. perfusion abnormalities, promptly, and continuous monitoring is the best option in clinical practice. The gastric mucosal systemic $P\mathrm{CO_2}$ (arterial blood) gradient best reflects mucosal perfusion. Also, gut perfusion decreases early in shock, often when systemic haemodynamics are stable.[23] Saline tonometry, and gas tonometry, both need repeated samples for arterial blood or saline $P\mathrm{CO_2}$. It is not feasible in

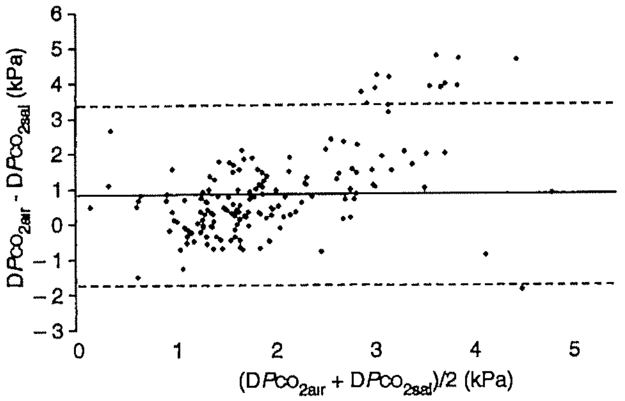

Fig 2 The agreement between $DPCO_{2gas}$ and $DPCO_{2sal}$ analysed using the method by Bland and Altman.[20] $DPCO_{2air}$=gastric mucosal end-tidal PCO_2 difference when mucosal PCO_2 was measured using gas tonometry. $DPCO_{2sal}$=gastric mucosal arterial PCO_2 difference when mucosal PCO_2 was measured using saline tonometry Solid line indicates bias of this comparison and dotted lines indicate ±2 SD of the bias.

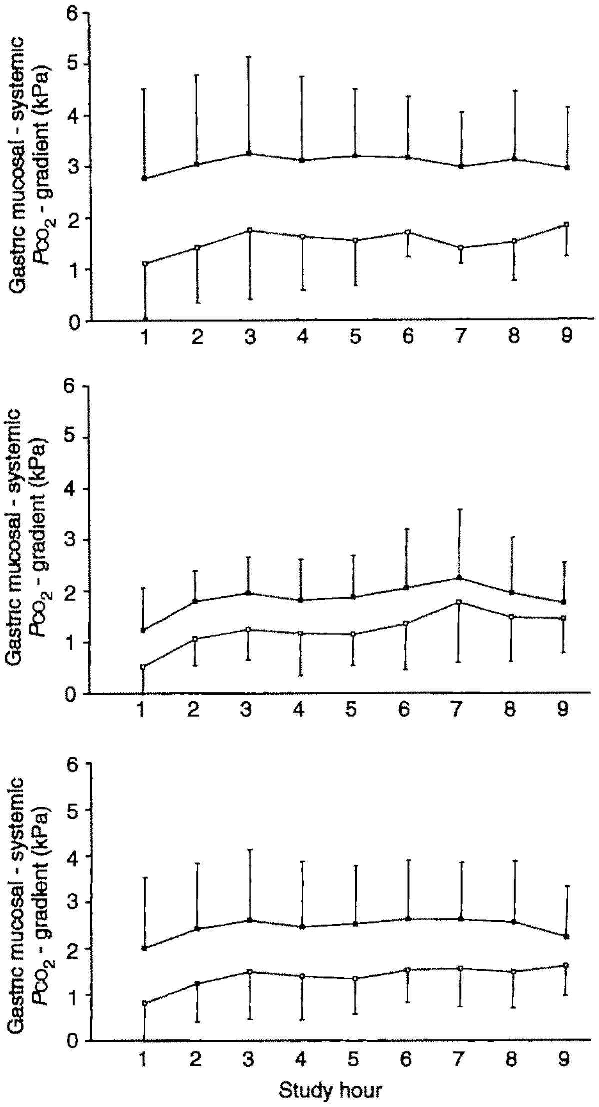

Fig 3 Gastric mucosal-systemic PCO_2 difference (mean (SD)) during the 8 h study period Gastric mucosal PCO_2 was measured using Tonocap® Open symbols = gastric mucosal-arterial blood PCO_2, closed symbols = gastric mucosal-end-tidal PCO_2. (Top) Patients with ALI; (middle) patients recovering from cardiac surgery; (bottom) all patients combined. When all patients were analysed together (bottom) using general linear model there was a significant effect of time ($P<0.001$) and group ($P=0.02$) but no time by group (arterial blood PCO_2 or end-tidal PCO_2) interaction ($P=0.9$).

clinical practice to draw and analyse arterial blood and gastric tonometer saline samples at frequent, e.g. 10–15 min intervals, if patients are clinically stable. However, because splanchnic perfusion deteriorates early in shock, this clinically stable phase of critical illness would be ideal to monitor gastrointestinal perfusion. The measurement of gastric mucosal-end-tidal CO_2 is a convenient method to continuously monitor gastric mucosal perfusion without a need to repeatedly analyse saline or arterial blood samples. Because no laboratory work is needed, several potential errors and problems related with sample handling and analysis are avoided. We used a separate monitor to analyse end-tidal CO_2 but a newer version of Tonocap® automatically analyses and displays both gastric mucosal and end-tidal PCO_2. Tonocap® (both mucosal PCO_2 and end-tidal PCO_2) has to be calibrated once every 2 months with a gas of known PCO_2. There is no need for recalibration after ventilatory adjustments and also temperature has no effect on the measurements. The potential problem of water evaporation in the tubing of capnograph is avoided because Tonocap® includes a water separation system which is based on a hydrophilic membrane.

We are not aware of any studies that have evaluated the gastric-mucosal end-tidal PCO_2 difference to assess splanchnic perfusion. There are several studies that examined the agreement between gastric mucosal PCO_2 measured by saline and gas tonometry.[14–16] In our study the correlation between gastric mucosal PCO_2 measured by saline and gas tonometry was not as good as has been reported elsewhere. We do not have a clear explanation for this discrepancy. Also, we do not know why gas tonometry systematically gave higher values than saline tonometry (Figs 6 and 8). We did not use H_2-blockers in our patients but this should not affect the agreement between the two methods. It is not clear if H_2-blockers are needed in critically ill patients to improve the performance of gastric tonometry.[20 21 24 25] In patients with cardiogenic shock, a systematic disagreement between saline and gas tonometry was found.[26] Under-correction of saline samples may be responsible although correction was done according to manufacturer's recommendations. We regarded saline technique as a gold standard but this may not necessarily be true.[27 28] *In vivo*, gas tonometry gave a closer agreement with the PCO_2 of the test solution.[27] Also, the bias between gas and saline tonometry was reduced by replacing saline by buffered electrolyte solutions.[27] We used saline with our conventional tonometry and this may have contributed to the differences in our study. The degree of clinically important disagreement between different

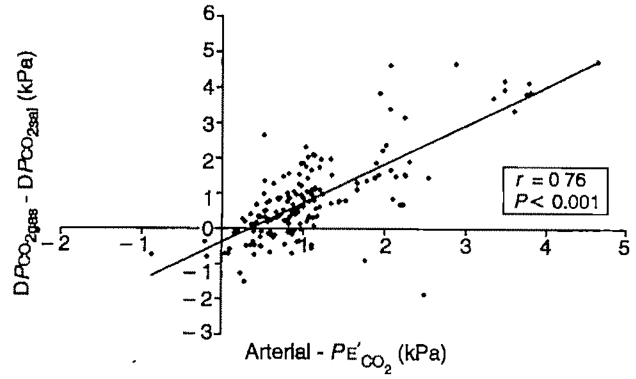

Fig 4 Correlation between arterial end-tidal $P\text{CO}_2$ difference (=arterial–$P\text{E}'_{\text{CO}_2}$) and $DP\text{CO}_{2gas}$–$DP\text{CO}_{2sal}$ difference. $DP\text{CO}_{2gas}$=gastric mucosal $P\text{CO}_2$–end-tidal $P\text{CO}_2$ when gastric mucosal $P\text{CO}_2$ is measured using gas tonometry. $DP\text{CO}_{2sal}$=gastric mucosal $P\text{CO}_2$–arterial $P\text{CO}_2$ when gastric mucosal $P\text{CO}_2$ is measured using saline tonometry.

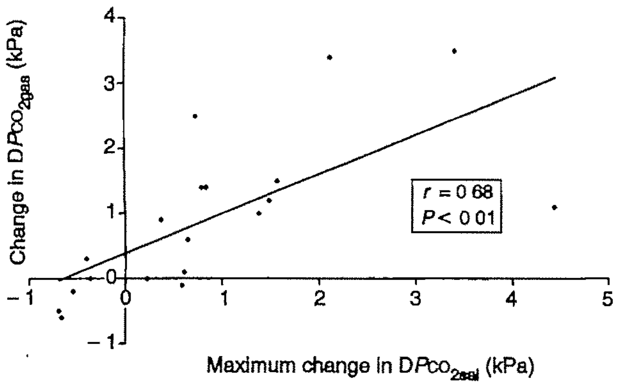

Fig 5 The maximum change from baseline in $DP\text{CO}_{2sal}$ and the corresponding change in $DP\text{CO}_{2gas}$. $DP\text{CO}_{2gas}$=gastric mucosal $P\text{CO}_2$–end-tidal $P\text{CO}_2$ when gastric mucosal $P\text{CO}_2$ is measured using gas tonometry. $DP\text{CO}_{2sal}$=gastric mucosal $P\text{CO}_2$–arterial $P\text{CO}_2$ when gastric mucosal $P\text{CO}_2$ is measured using saline tonometry.

methods to estimate mucosal perfusion is more important than the disagreement *per se*.

The normal gastric mucosal systemic $P\text{CO}_2$ difference is not known and more importantly we do not know how large a difference is clinically important in critically ill patients. In our previous study with healthy volunteers, the gastric mucosal arterial $P\text{CO}_2$ gap varied between 1.4 and 3 kPa depending on whether nasogastric suction or H_2-blockers were used.[20] A more recent study in healthy volunteers suggested a normal threshold value of <1.1 kPa for a gastric mucosal arterial $P\text{CO}_2$ difference.[29] Gastric mucosal $P\text{CO}_2$ depends on several factors such as aerobic and anaerobic production of CO_2 and also on perfusion of the gastric mucosa,[17] and it is not clear to what extent increased gastric mucosal $P\text{CO}_2$ indicates tissue hypoxia or decreased mucosal perfusion. A recent experimental study suggested that gastric mucosal $P\text{CO}_2$ has to increase to >13 kPa to indicate tissue hypoxia.[30] In our study the bias and the precision of the agreement between $DP\text{CO}_{2gas}$ and $DP\text{CO}_{2sal}$ were 0.85 and 1.25 kPa, respectively. Therefore, we propose, that the small disagreement between these methods may not be clinically important.

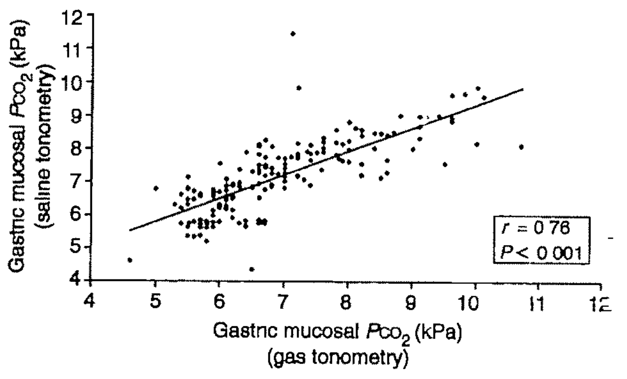

Fig 6 Correlation between paired gastric mucosal $P\text{CO}_2$ measurements when $P\text{CO}_2$ was measured simultaneously using both saline and gas tonometry

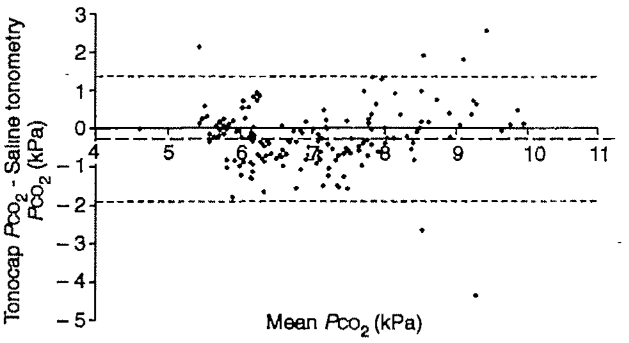

Fig 7 The agreement between simultaneous gastric mucosal $P\text{CO}_2$ measurements when both air (Tonocap®) and saline tonometry were used. Mean $P\text{CO}_2$=(Tonocap® $P\text{CO}_2$+saline tonometry $P\text{CO}_2$)/2. Analysis was done using the method by Bland and Altman [20] Solid line indicates bias of this comparison and dotted lines indicate ±2 SD of the bias.

One obvious problem with the use of the gastric mucosal end-tidal $P\text{CO}_2$ difference is that in patients with impaired gas exchange, end-tidal CO_2 does not represent arterial (and hence systemic) $P\text{CO}_2$.[19] In patients who do not have ALI this is not a large problem but in patients who have lung injury, end-tidal CO_2 may underestimate systemic $P\text{CO}_2$. We found that in patients who have ALI, $DP\text{CO}_{2gas}$ overestimated $DP\text{CO}_{2sal}$ more than in patients who do not have ALI. Figure 3 also shows that the disagreement between $DP\text{CO}_{2gas}$ and $DP\text{CO}_{2sal}$ increases as the arterial end-tidal $P\text{CO}_2$ difference increases (indicating increased dead space ventilation). However, for at least two reasons the potential overestimation of the gastric mucosal systemic $P\text{CO}_2$ difference is not a major clinical problem. First, it is physiologically obvious and easily recognizable. A significant difference between arterial blood $P\text{CO}_2$ and end-tidal CO_2, can be easily measured and used to interpret $DP\text{CO}_{2gas}$

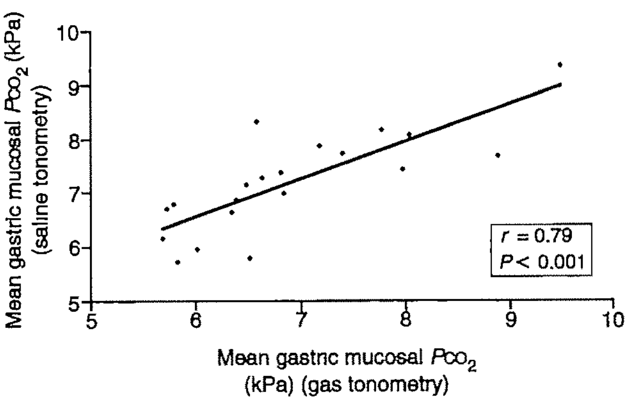

Fig 8 Correlation between the mean gastric mucosal $P\mathrm{CO}_2$ values calculated for each patient during the 8 h study period Measurements were done simultaneously both by air and saline tonometry.

Secondly, an overestimate of the gastric mucosal systemic $P\mathrm{CO}_2$ difference using $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ means that truly increased $P\mathrm{CO}_2$ differences will not be left undetected. We found that changes in $\mathrm{D}P\mathrm{CO}_{2\mathrm{gas}}$ reflected changes in $\mathrm{D}P\mathrm{CO}_{2\mathrm{sal}}$ during our study period, but the time period for our study was relatively short and probably was during steady state CO_2 production, lung function and dead space ventilation. Therefore, we cannot address the potential impact of changes in these variables during the progression of critical illness.

The difference between gastric mucosal end tidal $P\mathrm{CO}_2$ is a potentially useful method for continuous monitoring of splanchnic perfusion. It is easy to use and it does not require much additional work from staff, and the limits of the method are easy to assess and they do not jeopardize patient care. Studies of clinical outcome, based on interventions using this information are needed.

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LABORATORY INVESTIGATIONS

Inhibition of nitric oxide synthesis augments pulmonary oedema in isolated perfused rabbit lung

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The role of nitric oxide (NO) in precipitating pulmonary oedema in acute lung injury remains unclear. We have investigated the mechanism of involvement of NO in the maintenance of liquid balance in the isolated rabbit lung. Thirty pairs of lungs were perfused with colloid for up to 6 h, during which pulmonary vascular resistance (PVR) and capillary pressure (PCP) were measured frequently, and time to gain 5 g in weight (t_5) was recorded. Four protocols with different perfusate additives were studied: (i) none (control, n=11); (ii) 10 mmol N^G-nitro-L-arginine methyl ester (L-NAME) (n=6); (iii) 10 mmol L-NAME with 100 µmol lodoxamide, an inhibitor of mast cell degranulation (n=7); (iv) 10 mmol L-NAME with 10 µmol 8-bromo-3′,5′-cyclic guanosine monophosphate (8Br-cGMP), an analogue of cGMP that may reduce vascular permeability by relaxing contractile elements in endothelial cells (n=6). Neither PVR nor PCP differed between protocols. L-NAME markedly reduced t_5 from 248 (27) min (mean (SEM)) in protocol (i) to 144 (5) min in protocol (ii) (P<0.05). Both lodoxamide (t_5=178 (7) min) and 8Br-cGMP (t_5=204 (10) min) substantially corrected the effect of L-NAME (P<0.005). Results suggest that maintenance of a low permeability by NO may involve mast cell stabilization and endothelial cell relaxation.

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Septic shock is associated with a fall in systemic vascular resistance. There is interest in using inhibitors of nitric oxide synthase (NOS) systemically to correct this change, but concern that inhibition of NOS may exacerbate pulmonary hypertension and worsen pulmonary oedema. Hinder and colleagues[1] have used an animal model of sepsis to show that nitric oxide (NO) inhalation may protect against pulmonary oedema associated with endotoxaemia plus NOS inhibition. An important issue is whether NO has independent effects upon vascular pressures and microvascular permeability, which separately influence liquid balance across the vascular wall. NO has been shown to participate in the regulation of blood flow in a number of species and vascular beds,[2–6] and is, therefore, capable of changing the microvascular pressure that drives oedema formation. There is, in addition, growing evidence that NO may play a significant role in the maintenance of pulmonary fluid balance independently of its affects on vascular pressures. NO has been seen to protect the lungs from increased permeability during injury in a number of species. Inhaled NO in the isolated perfused rabbit lung reduced pulmonary vascular permeability caused by hydrogen peroxide injury.[7] In the rat lung the inhibition of NOS by N^G-nitro-L-arginine methyl ester (L-NAME) during hyperoxia potentiated injury, indicating a protective effect of NO.[8] Moore and colleagues demonstrated that NO prevented microvascular damage (measured as increases in permeability) after ischaemia-reperfusion injury in the guinea-pig lung.[9] There is also evidence that the basal release of NO helps to maintain normal pulmonary vascular fluid balance, while NO released during inflammation or injury increases vascular permeability.[10–12]

The mechanisms by which NO stabilizes microvascular permeability remain unclear. There is evidence for both a

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direct and an indirect effect of NO on the permeability of the epithelium and endothelium. NO may act directly on intercellular junctions by stimulating increases in 3′,5′-cyclic guanosine monophosphate (cGMP) which causes cellular relaxation. This may narrow intercellular junctions and there is evidence to suggest that it reduces permeability.[13] Alternatively, or additionally, NO has been shown to have a stabilizing effect on mast cells.[14] Mast cells are found at the host–environment interface and their activation results in the release of mediators (e.g. histamine) that have been associated with increased vascular permeability.[15]

It is unclear whether endogenous NO plays a role in the maintenance of basal pulmonary fluid balance, and if it does, by what mechanism. We used L-NAME, an inhibitor of NOS, to examine whether basal NO release helps to maintain a normal (control) rate of weight gain in the isolated perfused rabbit lung. The potential role of NO as a mast cell stabilizer was investigated with L-NAME and lodoxamide (a mast cell stabilizer). To examine the possible direct effect of NO on cGMP we utilized L-NAME and 8-bromo-cGMP (8Br-cGMP), an analogue of cGMP. Fortunately, in this preparation, changes in the rate of weight gain are observed in the absence of changes in microvascular pressure, thereby eliminating potential effects on weight gain of pressure changes alone.

Methods

Lung isolation and perfusion

This study was approved by the UK Home Office (Licence 30/01030). Male New Zealand White rabbits (body weight range 2.5–3.5 kg) were anaesthetized with 4–6 ml h^{-1} i.v. of a mixture of ketamine (30 mg ml^{-1}; Willows Francis Veterinary, Crawley, West Sussex, UK) and xylazine (6 mg ml^{-1}; Bayer, Bury St Edmunds, Suffolk, UK). A pneumothorax was effected by opening the diaphragm via a laparotomy and a midline thoracotomy was performed. The rabbit was ventilated via a tracheal cannula at 30 b.p.m. with a tidal volume of 15–20 ml and an inspiration:expiration ratio of 1:1. The rabbit was anticoagulated with 1000 u. i.v. heparin and exsanguinated via the carotid artery. The pulmonary artery was then isolated and cannulated and a non-recirculating flow of perfusate (5°C) with a flow of 10–20 ml min^{-1} was begun. The perfusate contained 137 mmol NaCl, 5.37 mmol KCl, 0.57 mmol KH_2PO_4 1.67 mmol $CaCl_2$, 0.81 mmol $MgSO_4$, 0.34 mmol Na_2HPO_4, 1.0 g litre^{-1} glucose (Hanks Balanced Salts, Sigma, Poole, Dorset, UK), plus 40 g litre^{-1} dextran and 20 g litre^{-1} bovine serum albumin. The lungs were excised from the thorax and suspended freely from a force transducer via the trachea (Pioden Controls Ltd, Lectromed, Letchworth, Hertfordshire, UK). Between 800 and 1000 ml of perfusate were allowed to flow through the lungs to wash out red blood cells. The left atrium was then cannulated via an incision in the left ventricle, and the perfusate recirculated.

The perfusion rate was slowly increased to 122–125 ml min^{-1}, the temperature was brought up to 38–40°C, the tidal volume was increased to 10 ml min^{-1} kg body weight^{-1} and the ventilation gas was changed from 100 to 21% oxygen, 5% carbon dioxide, balance N_2 (euoxic gas). The lungs were ventilated with a positive end-expiratory pressure of 2.0 mm Hg and a valve was inserted in the ventilator circuit to prevent inspiratory pressures from rising above 18 mm Hg. The pH of the perfusate was adjusted to the range of 7.37–7.42 with $NaHCO_3$. The left atrial pressure was set at 2.0–3.0 mm Hg (referred to zero pressure at the hilum of the lung) to ensure zone III conditions through much of the lung at end-expiration. The perfusate flowed through a gas exchanger prior to entry into the lung in order to maintain gas tension in the perfusate entering the lung within 4.7±3.6 mm Hg of that exiting the lung. Perfusate pH, $P\text{O}_2$ and $P\text{CO}_2$ were measured every 15 min in perfusate samples taken from the pulmonary arterial cannula (Instrumentation Laboratory 1306 Blood Gas Analyzer, Warrington, Cheshire, UK). Pulmonary arterial, left atrial, and airway pressures were measured via small-bore tubing threaded into the perfusion cannulae and the endotracheal tube, and connected to pressure transducers. Pulmonary vascular resistance (PVR) was calculated by dividing the difference between pulmonary arterial pressure and left atrial pressure by perfusate flow. Capillary pressures were measured using the double-vascular occlusion technique of Dawson and colleagues.[16] With this method, in-flow to the lung and out-flow from the lung are occluded simultaneously (the perfusate continues to flow around a bypass circuit), and the resulting equilibrium pressure in the lung at end-expiration is taken to be equal to the pulmonary capillary pressure. The perfusate was exchanged hourly. Experiments were terminated at 300 min or earlier if complete alveolar and airway oedema was present at end expiration, as indicated by a trachea full of liquid.

Protocol (i): controls (n=11)

Lungs were perfused for 300 min and ventilated with euoxic gas in order to establish the stability of the preparation.

Protocol (ii): L-NAME exposure (n=6)

As in protocol (i) but with 10 mmol L-NAME added into the perfusion circuit from 15 min.

Protocol (iii): L-NAME and lodoxamide exposure (n=6)

As in protocol (i) but with 10 mmol L-NAME and 10 µM lodoxamide added simultaneously from 15 min.

Protocol (iv): L-NAME and 8Br-cGMP (n=6)

As in protocol (i) but with 10 mmol L-NAME and 10 µmol 8Br-cGMP added simultaneously from 15 min.

Statistical analysis

Analysis of variance was used (SPSS for Windows, version 7.5) to compare the hourly rates of weight gain between the four groups. The pulmonary vascular resistance, capillary

Table 1 Perfusate Po_2 and Pco_2 (mm Hg), perfusate pH, and pulmonary vascular resistance (PVR, mm Hg ml^{-1} min^{-1}) averaged for the duration of the experiments from measurements every 15 min; also the time (t_5, min) from the beginning of the experiment to a cumulative weight gain of 5 g. Values are mean (SEM). * Denotes a significant difference from control (protocol (i)) ($P<0.009$). † Denotes a significant difference from L-NAME treated lungs (protocol (ii)) ($P<0.003$). ‡ Denotes a significant difference from L-NAME and lodoxamide treated lungs (protocol (iii)) ($P<0.045$)

Experimental condition	Po_2	Pco_2	**pH**	**PVR**	t_5
Protocol (i) (n=11)	128.4 (1.82)	32.7 (0.25)	7.377 (0.008)	7.83×10^{-2} (3.14×10^{-3})	248.1 (27.2)
Protocol (ii) (n=6)	133.5 (0.95)	32.9 (0.53)	7.364 (0.008)	7.58×10^{-2} (6.27×10^{-3})	144.3 (5.0)*
Protocol (iii) (n=7)	129.8 (0.81)	32.9 (0.53)	7.361 (0.008)	8.29×10^{-2} (3.35×10^{-3})	177.7 (6.8)†
Protocol (iv) (n=6)	127.4 (1.2)	33.1 (0.39)	7.376 (0.007)	6.77×10^{-2} (3.85×10^{-3})	204.4 (10.0)‡

Table 2 Capillary pressures averaged from measurements taken every 15 min via the double occlusion method (mm Hg). Values are mean (SEM). * Denotes a significant difference from protocol (i) ($P<0.03$)

Experimental condition	**Hour 1**	**Hour 2**	**Hour 3**	**Hour 4**	**Hour 5**
Protocol (i) (n=11)	5.19 (0.18)	5.64 (0.20)	5.87 (0.19)	5.89 (0.20)	6.07 (0.16)
Protocol (ii) (n=6)	4.85 (0.32)	4.89 (0.28)	5.29 (0.25)	7.40 (0.70)	N/A
Protocol (iii) (n=7)	5.29 (0.40)	5.67 (0.51)	5.81 (0.50)	6.84 (0.53)	N/A
Protocol (iv) (n=6)	5.79 (0.37)	5.86 (0.50)	5.82 (0.55)	6.28 (0.91)	7.66 (0.79)*

pressures, pH, Po_2 and Pco_2 were compared using analysis of variance with the Bonferoni correction.

Results

Control of perfusate gas composition and pH

Table 1 shows the perfusate Po_2, Pco_2 and pH for the duration of the experiment averaged from measurements taken every 15 min during each of the four protocols. Analysis of variance showed no significant differences between the four conditions.

Pulmonary vascular resistance

Table 1 shows the pulmonary vascular resistance averaged for the duration of each experiment, for the four groups. Analysis of variance showed no significant differences between the four conditions. Only one of the L-NAME-treated lungs (protocols (ii)–(iv)) completed the 300 min protocol; the other experiments were terminated prior to 300 min due to complete alveolar and airway oedema.

Capillary pressure

Figure 1 shows capillary pressure for each of the four protocols. Hourly mean values for each of the experimental protocols are given in Table 2. Analysis of variance showed no significant differences between the four conditions.

Weight gain

Figure 2 shows weight gain for the four protocols. Figure 2A compares protocols (i) and (ii); Figure 2B compares protocols (ii) and (iii); Figure 2C compares protocols (ii) and (iv); and Figure 2D compares protocols (iii) and (iv).

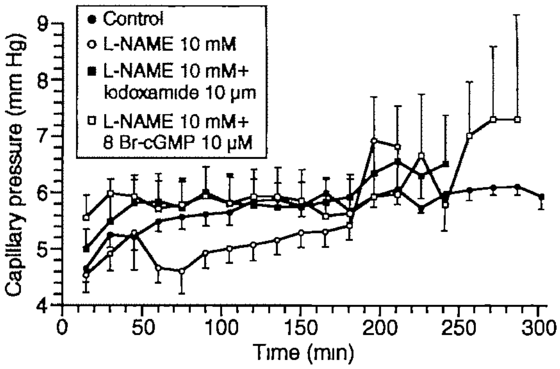

Fig 1 Capillary pressures measured by vascular occlusion at 15-min intervals in the four groups of isolated perfused rabbit lungs. Error bars represent SEM.

The addition of 10 mmol L-NAME into the perfusion circuit caused a dramatic and significant increase in the rate of weight gain in the third and fourth hour of the experiment ($P<0.016$ and $P<0.002$, respectively) as compared with control lungs; none of the L-NAME treated lungs survived into the fifth hour of the experiment due to oedema.

The addition of 10 mmol L-NAME significantly shortened the time it took for the isolated lungs to gain 5 g (see Table 1) ($P<0.009$) as compared with control lungs. The addition of 10 µmol lodoxamide with 10 mmol L-NAME (protocol (iii)) significantly delayed the time it took to increase lung weight by 5 g ($P<0.003$) as compared with lungs treated with L-NAME alone. The addition of 10 µmol 8Br-cGMP to L-NAME treated lungs (protocol (iv)) appeared to slow the time to 5 g even more effectively than the addition of lodoxamide ($P<0.0005$). Lungs treated

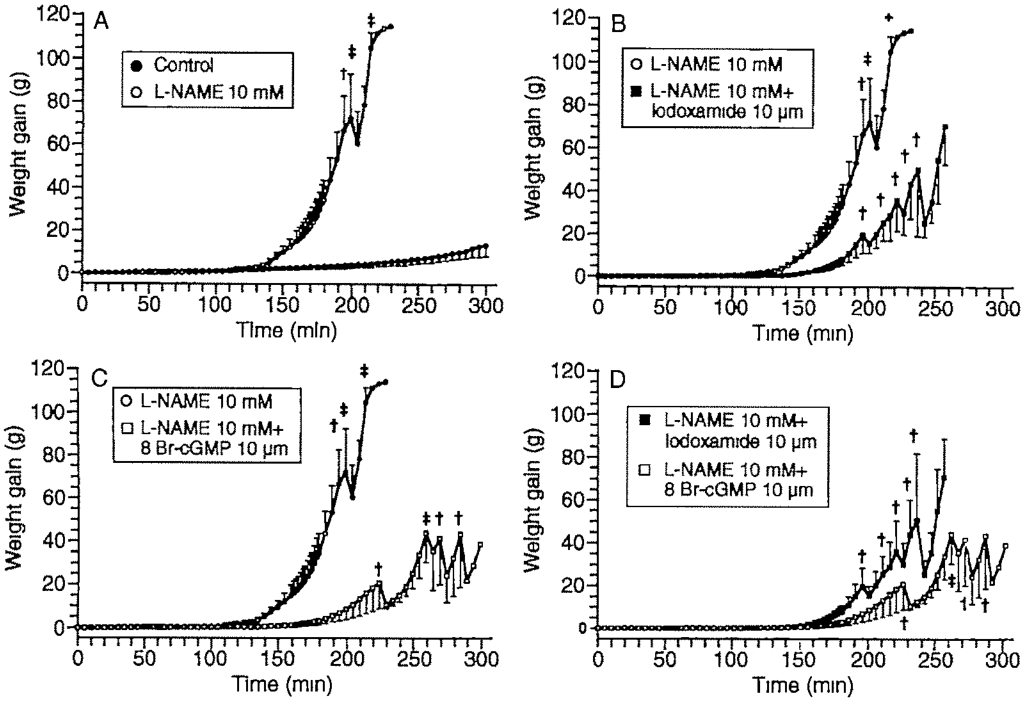

Fig 2 Weight gain in four groups of isolated rabbit lungs perfused at constant flow (A) Control (n=11) and 10 mmol L-NAME, (B) 10 mmol L-NAME and 10 mmol L-NAME with 10 µmol lodoxamide (n=7), (C) 10 mmol L-NAME and 10 mmol L-NAME with 10 µmol 8Br-cGMP (n=6); (D) 10 mmol L-NAME with 10 µmol lodoxamide and 10 mmol L-NAME with 10 µmol 8Br-cGMP Symbols above or below data indicate drop-out of experiments from a given group; †, one experiment, ‡, two experiments Error bars represent SEM.

with L-NAME and 8Br-cGMP took significantly less time to gain 5 g than did lungs treated with L-NAME and lodoxamide (P<0.045). Although lungs treated with L-NAME and lodoxamide reached 5 g significantly more quickly than control lungs (P<0.043), those treated with L-NAME and 8Br-cGMP were not significantly different from control. These data show 8Br-cGMP to delay the onset of L-NAME-induced weight gain more effectively than lodoxamide at the doses used.

Discussion

This study indicates that inhibition of NO with L-NAME dramatically enhances weight gain in isolated perfused rabbit lungs. This effect is not due to hydrostatic pulmonary oedema, as the inhibition of NO does not raise pulmonary vascular resistance, and more importantly, it does not change the capillary pressures from those found in control lungs. This study thus suggests a protective role for NO in the maintenance of normal pulmonary vascular permeability and further raises the possibility that NO has both a direct affect on vascular endothelial cells via cGMP as well an indirect effect of stabilizing mast cells.

The inhibition of NO with 10-mmol L-NAME did not change pulmonary vascular resistance significantly in this study. There is conflicting evidence in the literature as to the importance of endogenously released NO in maintaining a normal PVR. Inhibition of NO in isolated buffer-perfused rabbit-lungs as well as in open-chest rabbits raised the pulmonary arterial pressure.[17 18] L-NAME also caused increased PVR in the lungs of pigs, sheep, and humans.[19] However, there is evidence that the inhibition of NO does not affect pulmonary vascular tone in euoxic lungs. Lindeborg and colleagues found that L-NAME did not alter baseline pulmonary pressure in either blood or buffer perfused rabbit lungs.[20] Neither L-NAME nor L-NMMA affected baseline euoxic pulmonary arterial pressure in isolated blood perfused rat lungs.[21] Our study indicates that the baseline pulmonary vascular pressures seen do not result from production of NO. It may be that the disparate findings amongst the studies are due to species and preparation differences. Indeed a number of studies have advocated the importance of the red blood cell for the action of NO;[22 23] as we did not use erythrocytes in our preparation it could be that the lack of response to L-NAME was due to their absence.

An important finding of our study was that capillary pressures were not affected by the addition of 10 mmol L-NAME into the perfusion circuit. There is some disagreement as to the effects of NO on pulmonary capillary pressure. Some studies indicate that capillary pressure is lowered by NO while others find that NO has little or no effect. It has been shown in the isolated, perfused rabbit lung that inhaled NO, only affects the pre-capillary segment of the vasculature without significantly changing capillary pressure. Inhibition of NO production with L-NAME did not significantly affect capillary pressures as measured with double occlusion.[20 24] Benzing and colleagues saw that inhaled NO lowers capillary pressure in patients with adult respiratory distress syndrome.[25] L-NAME administration in thoroughbred horses caused a significant rise in pulmonary capillary pressures.[26] It has been suggested that NO serves a potential protective role in pulmonary liquid balance in that it acts to lower microvascular pressures, thereby reducing fluid filtration.[27] In our study, however, capillary pressures were unaffected by L-NAME, while the isolated lungs showed a dramatic increase in rate of weight gain. This implies that the increased weight gain seen in our experiments is not due to increased microvascular pressures causing hydrostatic oedema.

A mechanism by which NO may help to maintain normal pulmonary vascular permeability is by a direct action on endothelial cells. It has been known for some time that endothelial cells have the ability to contract.[28] They have been shown to possess actin and myosin, which play a central role in regulating the width of intercellular clefts.[29] Hence, the contraction of endothelial cells could increase vascular permeability. Calcium has been demonstrated to play a role in vascular integrity in the lung. In 1971, Nicolaysen[30] found that reducing intravascular calcium in perfused rabbit lungs resulted in pulmonary oedema. This role of calcium in endothelial cell contraction has been investigated more closely in recent years. In porcine pulmonary arterial and human umbilical vein endothelial cells it was shown that the formation of intercellular gaps was dependent on a rise in intracellular calcium and that the chelation of extracellular calcium caused cellular retraction.[28 29] Stimulation of calcium influx causes endothelial cell contraction and this is prevented by the elevation of cGMP (via 8Br-cGMP, atrial natriuretic factor or sodium nitroprusside).[31] NO has been shown to raise cGMP in endothelial cells by stimulating guanylate cyclase,[32] and NO has been found to decrease permeability in monolayers of bovine aortic endothelial cells.[13] The inhibition of NO synthesis by L-NAME also caused an increase in permeability in thrombin-stimulated human aortic and umbilical vein endothelial cells.[31] Hence, NO stimulates production of cGMP which, in turn, suppresses the elevation of intracellular calcium via cGMP-dependent protein kinase and elevates cAMP, which helps to regulate permeability.[31] In our study we found that the inhibition of NO production with L-NAME caused a significant increase in the rate of weight gain and that the addition of 8Br-cGMP attenuated this increase. In light of the previous research our findings may be interpreted as demonstrating a role for endogenous NO in the relaxation of endothelial cells; this relaxation is related to the elevation of cGMP levels.

NO may also be acting indirectly to help prevent pulmonary oedema by stabilizing mast cells. We have used lodoxamide to investigate this possibility. In isolated rat peritoneal mast cells[33] and human lung mast cells[34] lodoxamide has been shown to inhibit degranulation, as measured by release of histamine and prostaglandin D_2. Other studies have used mast cell protease activity[14] or tryptase release[35] to demonstrate inhibition of mast cells by lodoxamide. Other actions of lodoxamide in the lung that may contribute to its anti-inflammatory behaviour include inhibition of xanthine oxidase[36] and prevention of neutrophil accumulation.[37] Of considerable clinical interest, in the context of lung transplantation, has been the finding that lodoxamide reduces lung injury after ischaemia and reperfusion[38] and after re-expansion from a state of atelectasis.[37] The details of the mechanism of action of lodoxamide in preventing lung injury in these experiments remain uncertain.

There is evidence that NO stabilizes mast cells in the gut of various animal preparations. In the rat jejunum,[14] the feline small ileum,[39] and the rat duodenum[40 41] inhibition of NO synthesis caused a dramatic increase in permeability. In the rat jejunum, this increase was attenuated by the addition of either of two mast cell stabilizers (lodoxamide or doxantrazole), and identified as having a rapid component due to mast cell release of platelet activating factor, and a slower component due to mast cell release of histamine.[14] It has also been found that constitutive NO may play a role in mucosal protection in the jejunum.[42 43] Salvemini and coworkers have found that NO has an inhibitory effect on mast cells. [44] In our study we found that lodoxamide attenuates the increase in weight gain seen in isolated lungs exposed to L-NAME. This finding can be interpreted, in light of the cited evidence, to show that endogenous NO may stabilize mast cells in the isolated perfused rabbit lung. However, the beneficial effect of lodoxamide would also be consistent with its ability to inhibit xanthine oxidase, and thereby reduce oxidative damage to the lung. It would have been preferable in our own study to have performed additional experiments to identify whether mast cell degranulation had been inhibited by lodoxamide.

In conclusion, our study found that L-NAME caused a significant increase in rate of weight gain in the isolated perfused rabbit lung. This increase was attenuated by both lodoxamide and 8Br-cGMP, although 8Br-cGMP was slightly more effective at the dose used. All of these effects were independent of changes in pulmonary vascular resistance and capillary pressure. Future work could usefully examine the possibility that lodoxamide and 8Br-cGMP act synergistically. Indeed, Kimura and colleagues hypothesized that a reduction of cGMP could result in the degranulation of mast cells,[45] and it is known that mast cells themselves contain a constitutive calcium–calmodulin-dependent isoform of NOS.[46] Hence it may be that L-NAME in the isolated rabbit lung is reducing cGMP in endothelial cells and mast cells effecting both a constriction of the endothelial cell and a degranulation of the mast cell.

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Static versus dynamic respiratory mechanics for setting the ventilator

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The lower inflection point (LIP) of the inspiratory limb of a static pressure-volume (PV) loop is assumed to indicate the pressure at which most lung units are recruited. The LIP is determined by a static manoeuvre with a PV-history that is different from the PV-history of the actual ventilation. In nine surfactant-deficient piglets, information to allow setting PEEP and V_T was obtained, both from the PV-curve and also during ongoing ventilation from the dynamic compliance relationship. According to LIP, PEEP was set at 20 (95% confidence interval 17–22) cm H_2O. Volume-dependent dynamic compliance suggested a PEEP reduction (to 15 (13–18) cm H_2O). Pulmonary gas exchange remained satisfactory and this change resulted in reduced mechanical stress on the respiratory system, indirectly indicated by volume-dependent compliance being consistently great during the entire inspiration.

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Traditionally, three distinct features of the static pressure-volume (PV) loop of the respiratory system[1] are used to assess the mechanical stress imposed by artificial ventilation to the lung. The lower inflection point (LIP) of the inspiratory limb of the PV-loop is thought to indicate the pressure at which the majority of lung units are recruited.[2] The upper inflection point (UIP) indicates the pressure at which overdistension starts. The linear steep segment of the PV-curve between LIP and UIP is assumed to indicate the zone between end-expiratory collapse and overdistension although there is evidence that re-inflation of collapsed lung units continues above LIP and throughout the linear part of the PV-loop and perhaps even above UIP. Hence, it is hoped that lung injury from both shear stress and overdistension is avoided when tidal ventilation occurs on the linear segment of the PV-curve between LIP and UIP. This concept is intuitively appealing and it may improve ventilatory support in patients.[3] Recent studies have challenged these concepts, however,[4–10] as the mechanical properties of the respiratory system may depend on the pressure-volume history of the current tidal ventilation.[11] The assumption that information obtained from static manoeuvres like the PV-loop can be applied to tidal ventilation may be incorrect, given the pronounced differences in PV-history. Rather than studying the respiratory system under artificial conditions, we have assessed dynamic mechanics (slice-compliance)[12] during uninterrupted ventilation, and, hence, without affecting the actual PV-history of the lung. We analysed compliance within the tidal breath, taking into account the endotracheal-tube related flow-dependent resistance.

We studied surfactant-deficient piglets, and obtained information for setting PEEP and V_T both from the static PV-curve and from the slice-compliance technique. We compared settings of PEEP and V_T derived from static mechanics with those derived from the slice-compliance curve, in terms of the mechanical stress imposed to the

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respiratory system (end-inspiratory plateau pressure (P_{plat}) and the shape of the volume-dependent compliance curve), and gas exchange (arterial P_{O_2}).

Materials and methods

The investigations were performed at the experimental laboratories of the Department of Anaesthesiology and Intensive Care Medicine at the University Hospital of Uppsala, Sweden, and were conducted in conformity with the Helsinki convention for the use and care of animals. The Local Ethics Committee for Animal Experimentation reviewed and approved the study. We studied nine healthy male and female piglets of Swedish landrace breed (25 (SD 2) kg).

Anaesthesia and fluid management

Lavage

Lavage was performed as previously described[13 14] with 11 broncho-alveolar lavages (1.2–1.5 litres normal saline, corresponding to 50–60 ml kg^{-1}) which we have found causes a Pa_{O_2}/FI_{O_2} of <20 kPa. Between each lavage, the animals were ventilated for 5 min with pressure-controlled ventilation, FI_{O_2} 1.0, PEEP 15 cm H_2O and V_T 15 ml kg^{-1}. The effects of lavage on gas exchange, respiratory mechanics, and extravascular lung water (double-indicator dilution[15 16]) were compared between volume-controlled ventilation at ZEEP during healthy conditions and the surfactant-deficient conditions immediately after lavage. After lavage the animals were allowed to stabilize for 20 min.

Study design

After lavage, all animals underwent volume-controlled ventilation with the ventilator set according to both static (STAT) and dynamic (DYN) measurements, each setting being applied for 40 min (see Fig. 1). To compensate for time-related effects and to use the individual animals as their own controls, the animals were allocated randomly to settings by either method first. The effects of STAT and the DYN settings were also compared with the healthy conditions before lavage, with PEEP set to 4 cm H_2O (PEEP 4).

Ventilator and acquisition of pressure and flow data

The animals' lungs were ventilated through an endotracheal tube (#8, Mallinckrodt, Athlone, Ireland), connected by a 60 cm rigid tubing system to a Servo 300 ventilator (Siemens-Elema, Solna, Sweden). Airway pressure and flow were continuously measured with a pressure-flow transducer (BICORE CP100, Bicore Monitoring Systems, Irvine, CA, USA) placed between the tracheal tube and the ventilator circuit. The signals were sampled at 50 Hz and fed to a computer to be processed for the analysis of dynamic mechanics. Flow curves were continuously displayed and checked for ongoing flow at end-expiration as well as for any sign of respiratory muscle activity.

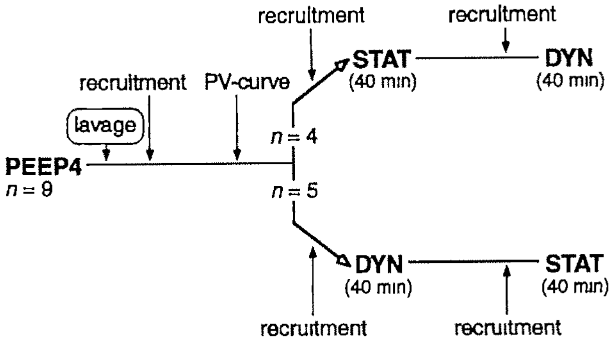


Fig 1 Schematic drawing of the study protocol. For further details please refer to the text

Static measurements for ventilator adjustment

Static mechanics were used to determine the LIP and the UIP for setting PEEP (at the level of LIP) and V_T (below UIP).

The lower inflection point of the static PV curve of the respiratory system was determined by a modified multi-occlusion technique[17] as follows: a recruitment manoeuvre (see below) was performed to standardize the PV-history of the lung. Ventilation was started at zero PEEP, frequency of 16 min^{-1}, I:E 1:1 and with constant inspiratory flow. Seven breaths with a V_T of 50 ml each were applied. At the end of the last breath, an end-inspiratory hold of 5 s was performed and the end-inspiratory airway pressure (P_{plat}) noted. For the next step, V_T was increased to 100 ml at otherwise identical settings. The procedure was repeated with V_T increased in steps of 50 ml up to 600 ml (corresponding to 24 ml kg^{-1}). The resulting values of plateau pressures after a 5 s end-inspiratory hold were used to construct the inflation limb of a static PV-loop (PV-curve) from which LIP and UIP were determined by tracing a straight line on the linear part as the best fit by eye.

Dynamic measurements for ventilation adjustment

Dynamic measurements were made to adjust the DYN settings and also to estimate indirectly the mechanical stress on the respiratory system after 40 min of ventilation at DYN and at STAT settings.

To detect non-linearities in dynamic respiratory system compliance within the tidal volume range, the slice method was used[12 18] which measures volume-dependent dynamic compliance and resistance breath by breath. The method continuously calculates tracheal pressure (P_{trach})[19] by subtracting the flow-dependent resistive pressure drop caused by the resistance of the endotracheal tube (ETT) from the pressure measured at the airway opening. The resulting P_{trach} $-V_T$ loop is divided into consecutive volume slices and mean compliance (intrinsic PEEP considered) and mean resistance (ETT resistance excluded) is calculated for each slice by repeated application of the linear

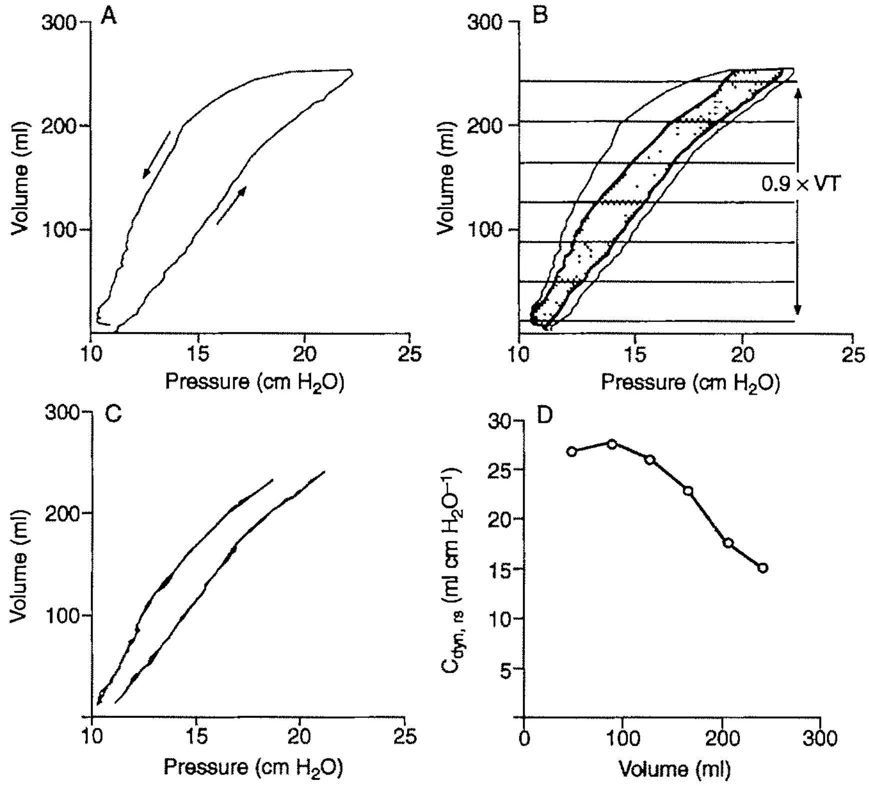
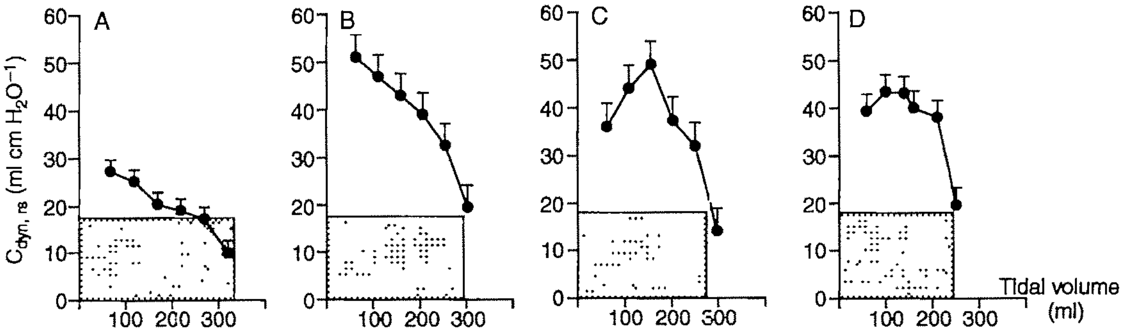


Fig 2 The slice-method (illustrated in one representative animal with surfactant deficiency) (A) Pressure as measured at the airway opening is plotted against volume (PAW/V-loop) Upward arrow denotes inspiration, downward arrow expiration. (B) The tracheal pressure P_{trach} (inner loop, dashed area) is calculated point by point according to reference 19. The pressure difference between the outer P_{AW}/V-loop and the inner P_{trach}/V-loop mainly represents the flow-dependent resistive pressure drop across the endotracheal tube (ETT). The pressure-flow relationship of the ETT used had been determined in the laboratory beforehand. The P_{trach}/V-loop is subdivided into eight slices (indicated by horizontal lines) and respiratory mechanics are analysed separately for each slice. The upper and lower 5% of the tidal volume (V_T) (i.e. slices 1 and 8, respectively) are excluded from analysis because of interference due to the ventilator's valve and the large volume acceleration. The remaining 90% of V_T are divided into 6 slices, each comprising 15% of V_T. One volume-dependent dynamic compliance and resistance of the respiratory system ($C_{rs,dyn}$ and $R_{rs,dyn}$) are calculated per slice (C) Quality check: P_{trach} is recalculated point by point for each slice, using the calculated values for $C_{rs,dyn}$ and $R_{rs,dyn}$ and the measured volume and flow. This recalculated P_{trach}/V-loop is superimposed on the measured P_{trach}/V-loop, and the pressure difference between both loops reflects the accuracy of the calculated mechanical parameters The measured and recalculated loops in C are barely distinguishable. (D) Plot of $C_{rs,dyn}$ over the slices of the tidal volume. The shape of this particular plot indicates overdistension after about one third of the tidal volume has been delivered (i.e. beginning with the third slice), reduction of V_T should be considered (Values are mean of 20 consecutive breaths, SD omitted for the sake of readability)

resistance-compliance model (RC-model). To reduce the effect of cardiac oscillations, the slice values of 20 consecutive breaths were averaged and used for the analysis (see Fig. 3; for the sake of clarity, the SD for each slice-compliance value is omitted in Figs 2 and 5). Combining the compliance and resistance values of all the slices gives the course of compliance and resistance within V_T (i.e. the volume-dependent compliance and resistance within one breath). The interpretation of the slice-compliance over V_T plots was as follows: the compliance curve represents the slope, i.e. the first derivative of the S-shaped PV-curve. The derivative of an S-shaped curve results in a trapeziform curve.[7] The lower bow of the S-curve is the ascending part and the upper bow is the descending part of the trapeziform compliance curve. The steepest middle segment of the S-curve is the horizontal and highest part of the compliance curve, which was the target of our DYN settings. The advantage of considering the derivative (compliance) curve rather than the original (PV) curve is that compliance, as a differential value, is very sensitive to changes in the shape of the PV-curve. A horizontal course of the dynamic slice-compliance within a single tidal volume suggests that a constant volume change per pressure change be obtained. If an ascending shape was present, PEEP was increased to see whether this resulted in a greater initial compliance level and a longer horizontal course of the compliance over the V_T. If a descending shape was found, an inappropriately high PEEP and/or V_T was assumed and adjustments were made (see below) to obtain a horizontal slice-compliance curve at a high absolute compliance level.

Before each study mode the animals' lungs were thoroughly suctioned. To make sure that any potential partial tube obstruction due to secretions or kinking had not influenced the results, the expiratory flow curves were



PEEP 20 cm H_2O
VT 330 ml
Pa_{O_2} 17 kPa
Pa_{CO_2} 5 8 kPa
SI 30 ml

PEEP 15 cm H_2O
VT 300 ml
Pa_{O_2} 18 kPa
Pa_{CO_2} 6 0 kPa
SI 45 ml

PEEP 13 cm H_2O
VT 280 ml
Pa_{O_2} 15 kPa
Pa_{CO_2} 6 2 kPa
SI 48 ml

PEEP 15 cm H_2O
VT 250 ml
Pa_{O_2} 18 kPa
Pa_{CO_2} 6.2 kPa
SI 46 ml

Fig 3 Representative plot (animal #8) of slice-compliance over tidal volume to illustrate the procedure for setting PEEP and tidal volume (A) Slice compliance ($C_{rs,dyn}$) starting from low level and the descending shape of the plot indicate overdistension at the onset of inspiration (B) A reduction of PEEP and V_T result in an increase in the level of $C_{rs,dyn}$, overdistension is still prominent. (C) A further reduction of both PEEP and V_T results in decreased $C_{rs,dyn}$, recruitment during the early phase of the delivery of V_T and overdistension continuing at end-inspiration. (D) An increase in PEEP results in a more horizontal shape of the compliance plot for the major part of the tidal volume, although there is still overdistension at end-inspiration. Grey area Tidal volume. Values are mean (SD) for 20 consecutive breaths). Settings and resulting gas exchange: (A) PEEP 20 cm H_2O, V_T 330 ml, Pa_{O_2} 17 kPa, Pa_{CO_2} 5.8 kPa, stroke index (SI) 30 ml, (B) PEEP 15 cm H_2O, V_T 300 ml, Pa_{O_2} 18 kPa, Pa_{CO_2} 6.0 kPa, SI 45 ml, (C) PEEP 13 cm H_2O, V_T 280 ml, Pa_{O_2} 15 kPa, Pa_{CO_2} 6 2 kPa, SI 48 ml; (D) PEEP 15 cm H_2O, V_T 250 ml, Pa_{O_2} 18 kPa, Pa_{CO_2} 6 2 kPa, SI 46 ml Please note: there is a 90-min interval between situation A and the final situation D during which the condition of the lung probably changes, affecting the shape of the plot in addition to changes in PEEP and V_T settings.

screened off-line, using a recently developed method.[20] This method analyses the time-constant of passive expiration as a function of the expired volume to detect tube obstruction.

Ventilator settings

Ventilatory frequency was 25 min^{-1}, FI_{O_2} 0.3, inspiration-to-expiration ratio 1:1 and inspiratory flow constant during all study modes.

Both mechanics as well as Pa_{CO_2} were taken into account for setting PEEP and V_T:

For the STAT settings, PEEP was set to the level of LIP, and V_T initially at 10 ml kg^{-1}. During the subsequent 40 min, blood gases were checked every 10 min and V_T was adjusted with respect to Pa_{CO_2}, while PEEP was adjusted with respect to the two point compliance of the respiratory system ($C_{rs,\,2P}$). If Pa_{CO_2} was above 6.5 kPa, V_T was increased in steps of 1 ml kg^{-1} until Pa_{CO_2} 5.5–6.5 kPa. With Pa_{CO_2} <5.5 kPa, V_T was reduced in steps of 1 ml kg^{-1}. Airway pressures were also measured every 10 min and $C_{rs,\,2P}$ was determined. If $C_{rs,\,2P}$ decreased to 90% or less of its initial level where PEEP=LIP, reduction of PEEP in steps of 2 cm H_2O was considered.

For the DYN settings, PEEP was initially set at 12 cm H_2O and V_T at 10 ml kg^{-1}, which we have found gives adequate gas exchange in most animals. During the subsequent 40 min, blood gases were checked and dynamic mechanics were analysed every 10 min, and PEEP and V_T were adjusted for an approximately horizontal shape of the slice-compliance curve. If an ascending shape of the slice-compliance appeared, PEEP was increased in steps of 2 cm H_2O. If a descending shape appeared, PEEP was reduced in steps of 2 cm H_2O. V_T was adjusted to keep the Pa_{CO_2} within 5.5–6.5 kPa and increased or decreased in steps of 1 ml kg^{-1}. (A representative example of the approach is given in Fig. 3.)

Respiratory mechanics determined at PEEP and VT after ventilator settings made using static/dynamic measurements

The end-inspiratory plateau pressure (P_{plat}) for both the STAT and the DYN settings was determined by performing an end-inspiratory hold for 5 s using the inspiratory hold function of the ventilator. The hold was performed with the V_T and the PEEP level applied that had been set according to static or dynamic mechanics.

Two point compliance of the respiratory system ($C_{rs,\,2P}$) was calculated according to the formula: Tidal volume/(end-inspiratory pressure – end-expiratory pressure). To measure the end-expiratory pressure, the expiratory hold function of the ventilator was used for 5 s. $C_{rs,\,2P}$ was determined with the V_T and the PEEP level applied that had been set according to static or dynamic mechanics, respectively. Intrinsic PEEP was considered when expiratory flow had not decreased to zero at end-expiration.

Re-expansion

The lungs were re-expanded immediately after lavage, as well as before STAT and DYN by a 5-min period of pressure-controlled ventilation with a frequency of 20 min^{-1}, I:E 1:1, FI_{O_2} 0.3, PEEP 25 and a peak inspiratory airway pressure of 50 cm H_2O. The re-expansion effect immediately after lavage was assessed in terms of $C_{rs,\,2P}$ setting the ventilator for 2 min to the pre-lavage PEEP 4 settings.

Monitoring

Intravascular catheters were surgically placed to measure central venous, pulmonary artery (via the external jugular vein), and aortic pressures (via the carotid artery). The position of the catheters was confirmed by pressure tracing. Cardiac output was determined from arterial thermodilution curves[21] (Pulsion Medical Systems, Munich, Germany). Unlike measurements of right heart flow with thermodilution in the pulmonary artery, arterial thermodilution is influenced minimally by ventilation-induced intrathoracic pressure changes. The anaesthetised-paralysed animals were studied in the physiological prone position. At the end of the experiment, the animals were killed with potassium chloride.

Anesthesia and fluid management

Anaesthesia was induced with an injection of tiletamine 3 mg kg^{-1}; zolazepam 3 mg kg^{-1}; xylazine 2.2 mg kg^{-1}; atropine 0.04 mg kg^{-1} intramuscularly and deepened with ketamine 100 mg, and morphine 1 mg kg^{-1} i.v. Anaesthesia was maintained with infusions of ketamine (20 mg kg^{-1} h^{-1}) and morphine (0.5 mg kg^{-1} h^{-1}), and muscle relaxation obtained by continuous infusion of pancuronium bromide (0.25 mg kg^{-1} h^{-1}). The animals were given a solution of 4.5 g $litre^{-1}$ NaCl with 25 g $litre^{-1}$ glucose (Rehydrex, Pharmacia Infusion AB, Uppsala, Sweden) at 10 ml kg^{-1} h^{-1} and a bolus of dextran-70 10 ml kg^{-1} (Macrodex 70, Pharmacia Infusion AB) to ensure normovolaemia.

Data presentation and statistics

Data are presented as mean (SD) or mean (95% confidence interval). Differences were evaluated with a non-parametric analysis of variance (Friedman test). Significant differences were evaluated using the paired sign test with correction for multiple comparisons,[22] and significance was accepted with $P \leq 0.05$. Where appropriate, the exact P value is also indicated.

Results

Effects of lavage

With lavage, EVLW increased from 7 (95% confidence interval 6–8) to 19 (15–21) ml kg^{-1}. Mean pulmonary artery pressure increased from 19 (13–22) to 34 (26–38) mm Hg, calculated venous admixture (Q_{va}/Q_t) increased from 4 (3–4.5) to 47 (38–55)%; $C_{rs,2P}$ decreased from 35 (29–41) to 14 ml cm H_2O^{-1}, and Pa_{O_2}/FI_{O_2} decreased from 72 (60–(8–16)88) to 12 (6–18) kPa, all determined at zero PEEP ($P \leq 0.01$ for all differences). The lower inflection point was 20 (17–22) cm H_2O (see Fig. 4 for the individual PV-curves). Upon re-expansion immediately after lavage, $C_{rs,2P}$ was 27 (20–36) ml cm H_2O^{-1} ($P \leq 0.05$ to PEEP 4).

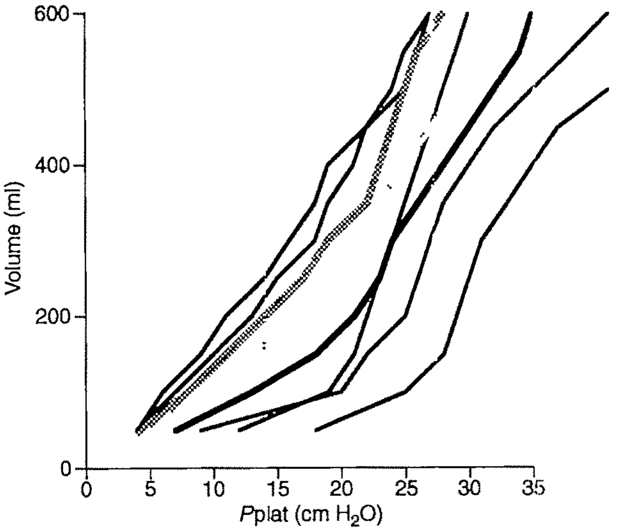


Fig 4 Pressure volume (PV) curves with lavage-induced surfactant deficiency. The curves for the individual animals are given.

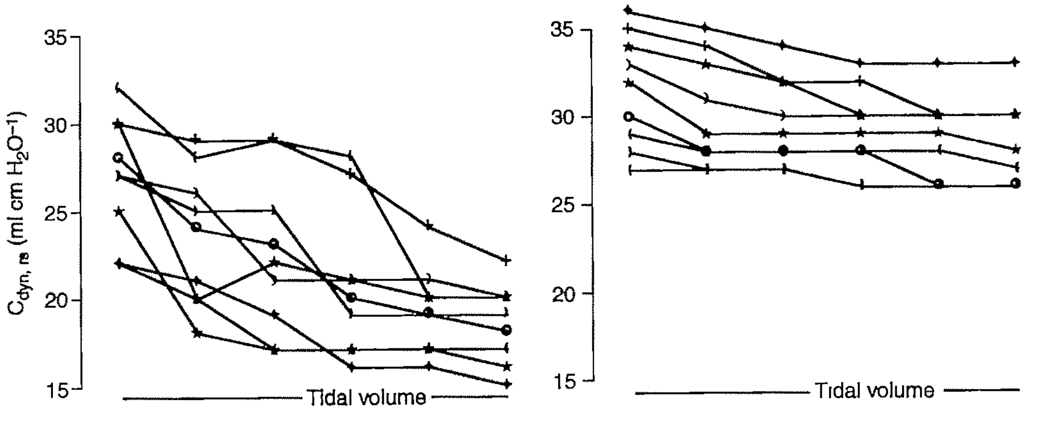


Fig 5 Slice compliance curves for individual animals after 40 min ventilation at STAT settings (left) and after 40 min of DYN settings (right) Symbols indicate individual animals, values are mean for 20 breaths (SD omitted for the sake of readability)

Table 1 Variables indirectly indicating alveolar recruitment and mechanical stress during ventilation of healthy lungs and at PEEP 4 cm H_2O (PEEP4), and with surfactant deficiency after 40 min ventilation at static (STAT) or dynamic (DYN) settings. Values are mean (95% confidence interval). The symbols denote: †, difference to PEEP 4; ††, difference to STAT at the significance levels indicated PIP, peak inspiratory airway pressure, MPAW, mean airway pressure; P_{plat}, end-inspiratory plateau pressure, $C_{rs,2P}$, two point compliance of the respiratory system; V_T, tidal volume; $S\bar{v}_{O_2}$, mixed venous saturation, CO, cardiac output, *Qva*/*Qt*, calculated venous admixture

	PEEP 4	STAT	DYN
PIP (cm H_2O)	17 (16–18)	40 (34–47)0.0001†	33 (26–39)0.0001† 0.002††
MPAW (cm H_2O)	9 (8–9)	25 (21–28)0.0001†	20 (16–23)0.0001† 0.05††
P_{plat} (cm H_2O)	13 (12–14)	35 (30–41)0.0001†	27 (22–32)0.0001† 0.002††
PEEP (cm H_2O)	4	20 (17–22)0.0001†	15 (13–18)0.0001† 0.001††
$C_{rs,2P}$ (ml cm H_2O^{-1})	35 (29–41)	21 (17–24)0.004†	28 (22–34)0.009† 0.008††
V_T (ml)	251 (236–266)	310 (297–323)0.0001†	296 (278–309)0.0001† 0.009††
Pa_{CO_2} (kPa)	5.8 (5.3–6.3)	6.0 (5.6–6.3)	6.2 (5.7–6.8)
Pa_{O_2} (kPa)	20 (19–22)	19 (17–20)0.03†	16 (14–18)0.008† 0.07††
$S\bar{v}_{O_2}$ (%)	65 (61–68)	53 (48–58) 0.006†	58 (54–68)
CO (ml kg^{-1})	179 (152–207)	164 (132–196)	202 (169–235) 0.008††
DO_2 (ml kg^{-1})	17 (15–19)	14 (12–17)0.07†	17 (14–20)0.008††
Q_{va}/Q_t (%)	3.9 (2.6–5.1)	4.6 (3.7–5.5)	8.3 (3.0–13.7)

Effects of settings according to dynamic mechanics versus static mechanics

According to the level of LIP, PEEP was set to 20 (17–22) cm H_2O during STAT settings, and 15 (13–18) cm H_2O ($P \leq 0.01$) during DYN settings (see Table 1 and Figs 5 and 6). As a result, P_{plat} was 8 cm H_2O less during DYN (27 (22–32) compared with 35 (30–41) cm H_2O during STAT; see Fig. 6). $C_{rs,2P}$ was 28 (22–34) with DYN and 21 (17–24) ml cm H_2O^{-1} with STAT, respectively ($P \leq 0.01$ for all differences). Pa_{CO_2} did not differ between STAT and DYN. Arterial PO_2 was 19 (17–20) with STAT and 16 (14–18) kPa with DYN ($P=0.07$ for the difference). During both settings Pa_{O_2} was less than under healthy conditions at PEEP 4 (Pa_{O_2}: 20 (19–22) kPa, $P \leq 0.05$ for the differences compared with STAT and DYN).

For the individual animals, V_T was 4.2 (5.5)% less with dynamic settings compared with static settings ($P \leq 0.05$).

An UIP immediately after lavage did not appear in all PV-curves. If present, it was 32 (28–36) cm H_2O (see Fig. 4 for the individual PV-curves). This corresponded to a rapidly descending shape of the slice-compliance curve. This shape was also quite often seen despite P_{plat}<UIP.

In all animals after 40 min of ventilation using STAT settings, the slice compliance curve showed a rapid decrease whereas it was nearly horizontal after 40 min of ventilation at DYN settings with only a slight tendency to decrease (see Fig. 5). Under no condition was intrinsic PEEP observed nor tube obstruction detected.

Cardiac index was greater with DYN (164 (132–196) during STAT, and 202 (169–235) ml min kg^{-1} during DYN, $P<0.01$), (see Fig. 6) as was oxygen delivery (14 (12–17) compared with 17 (14–20) ml min kg^{-1}, $P \leq 0.01$).

Discussion

We found that PEEP was set at 20 cm H_2O, if LIP was used, while dynamic mechanics suggested that a PEEP of 15 cm H_2O was sufficient to keep the lung open. This reduction of PEEP decreased P_{plat} and increased $C_{rs,2P}$. The dynamic compliance curve suggested that stress on the respiratory system was greater with STAT settings.

Critique of methods

The slice-compliance

There is increasing evidence that it is difficult, if not impossible, to infer the behaviour of lung units from the mechanical behaviour measured at the airway opening, i.e. from the PV-relation.[4–10] Why then do we measure respiratory system mechanics? One obvious motive is to indirectly estimate and reduce the mechanical stress to the respiratory system with appropriate ventilator settings. The PV-relation reflects the sum of all mechanical events occurring within the respiratory system and being transferred to the airway opening. Events at specific structures or regions of the lung will not be evident from this sum signal.[9] If the forces producing different mechanical events at different locations oppose each other, the resultant sum signal is difficult to analyse without far reaching assumptions about the relative contribution of those forces. Whether, for example, a particular volume is accommodated in the central airways, the terminal airways or the alveoli, and which of those structures are distended or overdistended by that volume cannot be derived from the PV-relation. However, some conclusions regarding the respiratory system as a whole can be drawn from the PV-relation. (1) A steep PV-relation (= high compliance) shows that insufflating the volume increment under study requires a relatively small pressure increment. No matter how the insufflated volume is distributed to the different lung structures, those lung structures that are filled will be subjected to a lower mechanical stress when compliance is great compared with a smaller compliance condition. (2) Since the PV-relation (and, consequently, the compliance)

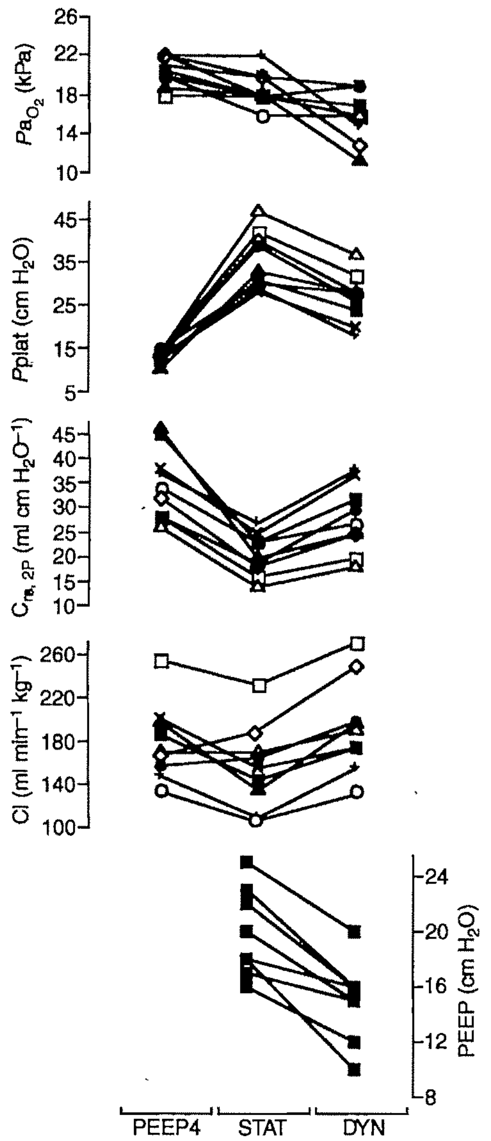


Fig 6 Indirect indicators of alveolar recruitment and mechanical stress during ventilation under healthy conditions (PEEP 4), and during ventilation at static (STAT) and dynamic (DYN) settings. Different symbols indicate individual animals. $C_{rs,2P}$, static compliance of the respiratory system; P_{plat}, end-inspiratory plateau pressure, CI, cardiac index.

may be non-linear over the tidal volume, the mechanical stress imposed to the respiratory system will be reduced if the entire V_T can be applied at a constant high compliance. (3) A decreasing compliance during the tidal volume inflation indicates increasing mechanical stress to the affected structure(s). (4) An increasing compliance could reflect different intrapulmonary events like, for example, opening of lung units during inspiration[6] or decreasing pressure requirements with increasing volume following the Laplace law or changes in the visco-elastic properties.[23] As a simple test, PEEP is increased: if this results in a higher compliance which is constant over a greater part of the V_T, the mechanical conditions of the respiratory system have probably improved (no matter what particular changes at what particular structures have brought about the improvement).

The slice-compliance does not include a model of the visco-elastic properties of the respiratory system. Generally speaking, visco-elastic properties can only be determined by changing from dynamic conditions to static ones. Such conditions are obtained with an end-inspiratory occlusion manoeuvre where the energy stored in visco-elastic elements during actual inspiration is released and can be estimated by the slow pressure decrease to the plateau pressure (although not unequivocally, since different time constants can also affect this pressure change). Visco-elasticity has been expressed as a spring-and-dashpot model.[23] Because the slice-compliance procedure does not model visco-elasticity, a small bias in favour of the STAT-settings may have been introduced since LIP is estimated during static conditions and, hence, without any visco-elastic pressure components.

Slice-compliance uses a linear RC-model successively applied to different volume slices, so that the linear RC-model is restricted to 1/8 of the volume range of the V_T. Using the linear RC-model repeatedly and separately for each of the consecutive slices preserves the robustness of the least-squares fit algorithm and analyses non-linearity, with the only assumption that this non-linearity can be divided into several consecutive, small and linear segments.

Limitations of the study

The determination of LIP by visual inspection (see Fig. 4) is inaccurate. Harris and colleagues have shown[24] that inter-observer variability determining inflection points visually can be considerable with a maximum difference of 11 cm H_2O for the same patient. An objective method for determining LIP would have strengthened our study.

With respect to the adjustment of PEEP one might ask whether these adjustments were fully comparable between dynamic and static settings. The LIP was determined before the study settings. Since the PV-manoeuvre is itself a kind of recruitment,[7 10] determining LIP repeatedly was not considered. Adjustments of PEEP during STAT settings would have been necessary if $C_{rs,2P}$ (determined every 10 min) had changed. When V_T was reduced to adjust for Pa_{CO_2}, $C_{rs,2P}$ increased slightly ($\leq$5%; data not given). A decrease in $C_{rs,2P}$, however, was never observed during the 40-min period with static settings. Therefore we did not test the assumption that this would have indicated overdistension and required a PEEP reduction. We might have found that increasing V_T (obtaining lower $C_{rs,2P}$) and decreasing PEEP in order to maintain $C_{rs,2P}$, as foreseen in the study protocol, might have produced end-expiratory collapse, and this would have revealed that, in retrospect, the protocol in this particular point was not based on a sound physiological rationale. Instead, PEEP, once set at the level of LIP, did not have to be changed during the STAT settings, nor was there ever any need to increase V_T to obtain normocapnia. The determination of LIP was not repeated since the PV-manoeuvre is stressful. A potential change in lung mechanics during the 40-min period of application could, therefore, have gone unnoticed.

The current study did not include oesophageal pressure data. In patients, LIP can be affected by chest wall mechanics.[25 26] We cannot exclude the possibility that the high LIP was also influenced by chest wall mechanics.

Finally, the number of animals was too small to definitely exclude any difference in Pa_{O_2} between STAT and DYN, and we acknowledge that with more animals the tendency of Pa_{O_2} to decrease with DYN settings could be a relevant difference between both settings. (To detect a true difference in Pa_{O_2} of 2 kPa with 0.70 power and a SD of 3 kPa for Pa_{O_2}, 28 animals would have been necessary.)

Titrating PEEP during actual ventilation

It was not surprising that the (indirect) indicators of mechanical stress at end-inspiration ($C_{rs,2P}$ and P_{plat}) were less with the lower PEEP during DYN settings (see Fig. 6). Neither $C_{rs,2P}$ nor P_{plat}, however, reflect non-linearities of compliance during the course of inspiration. The assumptions for using LIP as a guide to optimal PEEP are (1) that inspiratory compliance during actual ventilation is as linear as is the compliance above LIP for the static circumstance, and (2) that this linear segment of the static PV-curve indicates complete alveolar recruitment. The latter assumption has been challenged.[4 5 7–10] As regards the assumption of a linear compliance during the inspiratory phase of the actual ventilation, our data suggest that using the static PV-curve for setting PEEP (and V_T) results in pronounced non-linearities of the compliance, and the decreasing shape of the compliance curve indirectly suggests that inspiratory mechanical stress was higher with the STAT settings (see Fig. 5). In contrast, after 40 min of ventilation at DYN settings the slice compliance was greater and had a more horizontal shape (see Fig. 5). Adjustments of ventilator settings based on slice-compliance analysis are possible during uninterrupted ventilation, which is an advantage compared with the static approach which needs an artificial manoeuvre for constructing the PV-curve. Although clinical extrapolation is premature, these data challenge the uncritical use of the static PV-loop for making ventilator settings. Studies in which PEEP was set according to LIP and to a rather high level[3] found reduced mortality, but whether this was due to an 'open lung' condition, i.e. to a reduction of mechanical stress during the entire ventilatory cycle, or to other PEEP effects, as yet unclear, has not been shown. The static conditions are so different from those of actual ventilation that it is hard to imagine how and why the former should apply to the latter. The difference between PEEP according to the LIP level and PEEP according to slice-compliance most likely reflects the different PV-history of the respiratory system during static compared to dynamic conditions.

Assessment of full alveolar recruitment

Our case is based on evidence for full alveolar recruitment, which can only be estimated indirectly. Different indicators for alveolar recruitment have been used,[27–29] and in the current study, in addition to $C_{rs,2P}$ upon re-expansion immediately after lavage, Pa_{O_2} was used despite evidence for a weak association of oxygenation and respiratory mechanics.[30] With oxygenation and $C_{rs,2P}$ at (or near) its healthy level, full alveolar recruitment is likely. In our lavage-model, rigorous recruitment manoeuvres precede the ventilatory patterns under study and full alveolar recruitment is probably thereby achieved.

The Pa_{O_2} reduction of 3 kPa during dynamic settings compared with static settings was inconclusive (P=0.07 for the Pa_{O_2} difference STAT *vs* DYN, see Fig. 6 and Table 1). The small number of animals precludes definite conclusions. We assume, however, that functioning lung units were not de-recruited with the lower PEEP during DYN. First, lowering airway pressures during DYN increased cardiac output (see Fig. 6) which, as described by Dantzker and co-workers,[31] might increase shunt and, hence, reduce Pa_{O_2}. However, no major increase in venous admixture was observed (see Table 1). Also, we have found that in the porcine lavage model critically low Pa_{O_2} values rapidly develop once the airway pressure is below the threshold to keep the lung open. If the PEEP-reduction during DYN had induced local alveolar closure, we would have expected rapid progress to major collapse with life-threatening hypoxaemia. For this reason we considered a 40-min period sufficient for assessing short-term effects of different ventilator settings. The beneficial short-term circulatory effects of the DYN setting were not unexpected. Those effects have certainly a very limited impact on barotrauma / volutrauma, which is the clinically more relevant outcome variable but can only be studied in long-term experiments.

Titrating V_T

The study protocol also included adjustments of V_T (see Fig. 3) according to mechanical and blood gas criteria, but we never had to increase V_T. (Strictly speaking, changes in volume at constant frequency and inspiratory time always imply changes in inspiratory flow, too, but the potential effect of each of these effects could not be evaluated separately.) The UIP derived from static mechanics indicated overdistension at higher pressure levels than dynamic mechanics did: during STAT settings, P_{plat} (35 cm H_2O) was clearly above the UIP of about 32 cm H_2O, and this corresponded to a rapidly descending part of the slice-compliance plot. However, even when P_{plat} was below UIP, we frequently found a descending slice-compliance curve, indicating overdistension, which would not have been inferred from consideration of the UIP.

We conclude that in the atelectasis-prone porcine surfactant-deficient model, non-invasive analysis of volume-dependent dynamic compliance showed that, for keeping the lung open during ventilation, PEEP could be set 5 cm H_2O lower than LIP. With pulmonary gas exchange maintained at an appropriate level, this gave a greater two-point compliance of the respiratory system ($C_{rs,2P}$), smaller end-inspiratory plateau pressure (P_{plat}), and greater slice-compliance with a more horizontal course, all indirectly suggesting less mechanical stress to the respiratory system.

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Morphine tolerance increases [^{3}H]MK-801 binding affinity and constitutive neuronal nitric oxide synthase expression in rat spinal cord

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N-Methyl-D-aspartate (NMDA) receptor antagonists and nitric oxide synthase (NOS) inhibitors inhibit morphine tolerance. In the present study, a lumbar subarachnoid polyethylene (PE_{10}) catheter was implanted for drug administration to study alterations in NMDA receptor activity and NOS protein expression in a morphine-tolerant rat spinal model. Antinociceptive tolerance was induced by intrathecal (i.t.) morphine infusion (10 µg h^{-1}) for 5 days. Co-administered (+)-5-methyl-10,11-dihydro-^{5}*H*-dibenzo[*a,d*]cyclohepten-5,10-imine maleate (MK-801) (10 µg h^{-1} i.t.) with morphine was used to inhibit the development of morphine tolerance. Lumbar spinal cord segments were removed and prepared for [^{3}H]MK-801 binding assays and NOS western blotting. The binding affinity of [^{3}H]MK-801 was higher in spinal cords of morphine-tolerant rats (mean (SEM) K_D=0.41 (0.09) nM) than in control rats (1.50 (0.13) nM). There was no difference in B_{max}. Western blot analysis showed that constitutive expression of neuronal NOS (nNOS) protein in the morphine-tolerant group was twice that in the control group. This up-regulation was partially prevented by MK-801. The results suggest that morphine tolerance affects NMDA receptor binding activity and increases nNOS expression in the rat spinal cord.

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Two possible mechanisms of opioid tolerance, receptor uncoupling and receptor down-regulation, have been demonstrated.[1 2] Larcher and colleagues[3] proposed that activation of the NMDA-dependent pain-facilitatory systems may also play another possible mechanism of morphine tolerance. There is a growing body of evidence that opioid tolerance can be inhibited or attenuated by both competitive and non-competitive NMDA receptor antagonists in several animal models.[4–7] It has been proposed, therefore, that NMDA receptor activation plays a role in the development of morphine tolerance.[5 8] Recently, we have shown that NMDA receptor antagonists inhibit the development of morphine tolerance and affect µ-opioid receptor binding.[9] However, the effect of development of morphine tolerance on NMDA receptor-binding activity has not been studied.

Nitric oxide, an intracellular messenger linked to NMDA receptor activation, also plays a role in morphine tolerance.[8] NOS inhibitors attenuate or prevent morphine tolerance.[10–13] NOS activity is increased in chronic morphine-treated mouse brains[14 15] and the NOS mRNA level is greater in morphine-tolerant rat spinal cords than in controls.[16] However, it is not clear which NOS protein isoform is involved in the morphine tolerance.

In the present study, we examined the involvement of NMDA receptors and NOS in the development of morphine tolerance in the rat spinal cord.

Materials and methods

Animal preparation and intrathecal catheter implantation

With institutional approval, male Sprague–Dawley rats weighing 300–350 g were anaesthetized with chloral hydrate 400 mg kg^{-1} i.p., and a PE_{10} intrathecal (i.t.) catheter implantation was performed as previously described.[9] Rats were housed in the Animal Facility of the National Defense Medical Center for recovery after surgery. Three days after catheterization, a mini-osmotic pump

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(model 2001; Alzet, Palo Alto, CA, USA) with a pump rate of 1 μl h^{-1} for 7 days was first filled with morphine or other test drugs and implanted subcutaneously under chloral hydrate anaesthesia (400 mg kg^{-1} i.p.) between the scapulae. Rats with gross neurological injury or those in which fresh blood was found in the cerebrospinal fluid were excluded from the study.

Tail-flick test and induction of morphine tolerance

The tail-flick test was used to measure antinociception. All tests were performed daily for 5 days and 30 min before osmotic pump implantation. The tail-flick test was performed every 90 s, and the latencies were expressed as the average of four measurements over a 10 min test period in each rat. The heat intensity used was the average latency (3.1 ± 0.2 s) of 40 opioid-naive rats.

Tolerance, defined by a loss of the antinociceptive effect of morphine infusion as shown by the tail-flick test, was induced by morphine infusion (10 μg h^{-1} i.t.) for 5 days. MK-801 (10 μg h^{-1} i.t.) co-administered with morphine (10 μg h^{-1} i.t.) infusion was used to inhibit the development of tolerance.[9] Control animals were given equal amounts of saline (1 μl h^{-1} i.t.) or MK-801 (10 μg h^{-1} i.t.).

Membrane preparation and [^{3}H]MK-801 binding assays

On day 5, rats were killed and the lumbosacral segments of the spinal cords were collected. The segments of spinal cords were homogenized with a PT20 polytron in 50 mM Tris–acetate buffer (pH 7.4 at room temperature), then centrifuged (35 000*g* for 15 min at 4°C) twice. The pellets were resuspended in 50 mM Tris–acetate buffer, frozen in a methanol bath chilled with dry ice, thawed at room temperature and centrifuged again to remove excess endogenous excitatory amino acids. The pellets were resuspended in 50 mM Tris–acetate buffer, incubated at 37°C for 20 min and centrifuged again (35 000*g* for 20 min).

The method of [^{3}H]MK-801 saturation binding was modified from a previous study[17] and is briefly described below. [^{3}H]MK-801 (0.1–60 nM) was used as the radiolabelled ligand. Equilibrium binding was conducted in the presence of unlabelled NMDA (100 μM), glycine (10 μM) and spermidine (50 μM) at room temperature for 4 h. Nonspecific binding was determined in the presence of unlabeled MK-801 (10 μM). The incubation volume was 1 ml and the protein concentration was adjusted to 150 μg per tube. To stop binding, the rapid filtration method was used with a semi-automatic cell harvester (model 11021; Skatron Instruments, Sterling, VA, USA). All samples were incubated with scintillation cocktail overnight and then counted in a β-counter.

Western blot analysis of NOS protein expression

The frozen dorsal part of lumboscaral spinal cord segments were also prepared in cold extraction buffer (50 mM Tris–HCl, 1 mM EDTA, 1 mM phenylmethylsulphonyl fluoride, pH 7.4) homogenized and centrifuged (13 500 rpm, 45 min, 4°C) for NOS western blotting. Samples, containing 5–10 μg protein, were denatured in sample buffer (50 mM Tris–HCl, 10% glycerol, 2% sodium dodecyl sulphate (SDS), 100 mM dithiothreitol, pH 6.8) and heated for 5 min. An equal amount of protein (5–10 μg) was loaded on 6–7.5% SDS–polyacrylamide gel to separate NOS by electrophoresis (120 V, 4°C) and then transferred (250 mA, 4°C) to a nitrocellulose membrane (Millipore). Membranes were then blocked with 5% non-fat milk in phosphate buffer–0.1% Tween (PBST) for 1 h at room temperature and incubated with mouse monoclonal antibody to nNOS or of inducible NOS (iNOS) (1:2500 dilution; Transduction Laboratories, Lexington, KY, USA) in PBST (0.1% Tween) overnight at 4°C. The membranes were then washed with PBST (0.2% Tween) and incubated with anti-mouse IgG conjugated to horseradish peroxidase (1:10 000) for 1 h at room temperature. NOS proteins were visualized with a horseradish peroxidase enhanced chemiluminescence (ECL) kit (Amersham, Arlington Heights, IL, USA). Prestained protein standards (Bio-Rad) and positive control for nNOS or iNOS (Transduction Laboratories, Lexington, KY, USA) were used for molecular weight determinations and protein identification. The density of NOS bands was quantified by densitometric scanning (Image-Pro Plus software); the density of the other bands on a gel were expressed relative to that of the nNOS band (150 kDa) in the control group, which was defined as 100%.

Data analysis

All data are presented as mean (SEM) for the given number of rats or binding assays performed. All the receptor-binding assay data were analysed as described previously;[9] the program used involves a nonlinear, least-squares curve-fitting algorithm and assumes the simultaneous contribution of one or more independent binding sites. For statistical analysis, all data were initially analysed by analysis of variance, followed by the Student–Newman–Keuls *post hoc* test for multiple comparisons. $P<0.05$ was taken to indicate a significant difference.

Results

As in our previous study,[9] continuous morphine infusion (10 μg h^{-1} i.t.) induced antinociceptive tolerance on day 2. Continuous MK-801 infusion (10 μg h^{-1} i.t. for 5 days) alone did not produce any antinociception, but co-administration of MK-801 (10 μg h^{-1} i.t.) with morphine attenuated morphine tolerance (Fig. 1). In [^{3}H]MK-801 saturation binding assays, which measure NMDA receptor-

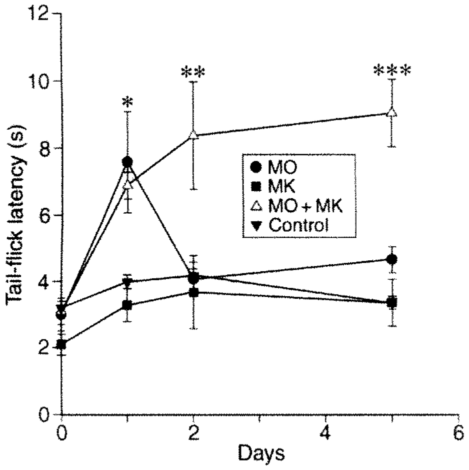

Fig 1 The effects of MK-801 on the development of morphine tolerance. Morphine tolerance (MO) was induced by continuous infusion (10 µg h^{-1} i.t.) for 5 days. The effect of MK-801 on morphine tolerance was examined by co-administering MK-801 10 µg h^{-1} i.t. (MO+MK) with morphine for 5 days. The antinociceptive effect of continuous MK-801 10 µg h^{-1} i.t. infusion (MK) was also examined. The control group was infused with the same amount of normal saline. Tail-flick latencies were measured daily for 5 days. All data points are averages of results from ≥10 rats, and the results are expressed as means±SEM. *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with the morphine-infused group.

gated ion channel activity, [^{3}H]MK-801 binding affinity in tolerant rat spinal cords (K_D=0.41 (0.09) nM) was four times that in control rats (K_D=1.50 (0.13) nM) (Fig. 2). A tendency to reduction in the receptor density, B_{max}, of [^{3}H] MK-801 binding was observed in tolerant rats, but the difference was not significant (Table 1). In the nNOS western blot analysis, a significant increase in constitutive expression of nNOS protein was observed in morphine-tolerant rats; this was partially attenuated by MK-801 co-administration (10 µl h^{-1} i.t.). Normal saline (1 µl h^{-1} i.t.) and MK-801 (10 µl h^{-1} i.t.) infusion alone did significantly affect nNOS expression (Fig. 3). In the present study, expression of iNOS protein was not detectable.

Discussion

The present study shows that long-term intrathecal infusion of morphine produced antinociceptive tolerance accompanied by an increase in the K_D of [^{3}H]MK-801. Up-regulation of nNOS expression was also observed in the dorsal horn of morphine-tolerant rats. Co-administration of MK-801 attenuates morphine tolerance assessed using the tail flick test in the rat spinal model as reported in previous studies.[4 5 7 9] Changes in [^{3}H]MK-801 binding and nNOS expression can be partially inhibited by MK-801 co-administration. These results suggest that activation of the NMDA receptors and their downstream signal transduction messenger, nitric oxide, are probably involved in another mechanism of morphine tolerance besides the µ-opioid receptor uncoupling from the G-protein and receptor down-regulation.[1 2]

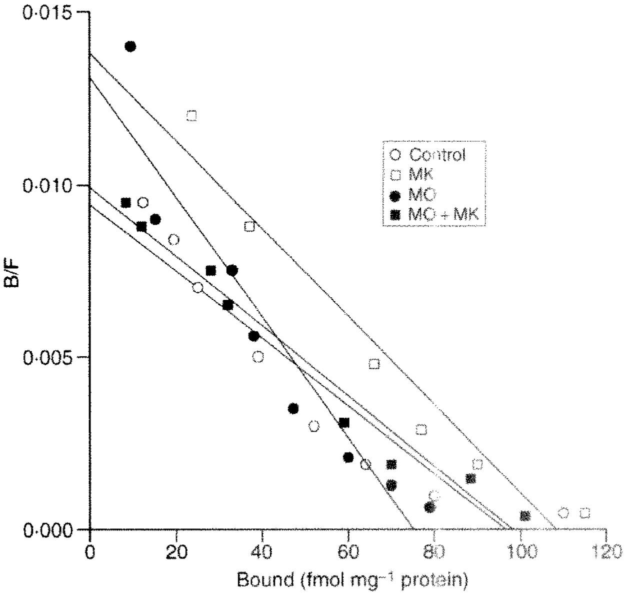

Fig 2 Scatchard analysis of [^{3}H]MK-801 binding in rat spinal cord membranes with various i.t. drug infusions. Rats were continuously infused with saline (control), morphine 10 µg h^{-1} (MO), MK-801 10 µg h^{-1} (MK) or a combination of morphine and MK-801 10 µg h^{-1} (MO+MK) for 5 days. Rats were killed and their spinal cords removed on the sixth day. Membranes were prepared for [^{3}H]MK-801 binding assays. [^{3}H]MK-801 (0.1–60 nM) was used as the radiolabelled ligand in the presence of glycine (10 µM) and NMDA (100 µM). Unlabelled MK-801 (10 µM) was used to determine nonspecific binding. Data points are from one of the six experiments, each with three-pooled lumbosacral segments of spinal cords and performed in triplicate.

From the results of the NMDA receptor-binding assays, morphine tolerance was associated with a significant increase in the probability of [^{3}H]MK-801 binding to the ligand-gated NMDA receptor channel. It may be reflected by an increase in the [^{3}H]MK-801 binding affinity in morphine tolerant rats, and this was prevented by MK-801 co-administration during the induction of morphine tolerance. The results suggest that continuous i.t. morphine infusion may make NMDA receptor channels open for longer or more often, thus enhancing the downstream production of nitric oxide. Collectively, these findings suggest that the activated NMDA–nitric oxide system may be involved in pain facilitation or may indirectly affect the µ-opioid receptor conformation, thus reducing the antinociceptive effect of morphine. However, Gudehithlu, Reddy and Bhargava[18] did not find any changes in the [^{3}H]MK-801 binding of tolerant rat spinal cords in the absence of glutamate and glycine in the binding assay buffer. The difference might result from receptor binding assay conditions; in our study, NMDA and glycine were added for [^{3}H]MK-801 saturation binding. It has been shown that NMDA and glycine are necessary for [^{3}H]MK-801 saturation binding but do not alter receptor density.[19] Therefore, it is reasonable to suggest that the NMDA receptor channel blocker, MK-801, attenuates the development of morphine tolerance by inhibiting the activity of

Table 1 Scatchard analysis of [^{3}H]MK-801 saturation binding in the rat spinal cord lumbosacral segment of rats treated with various drugs. The rat spinal cord lumbosacral segments were removed on the sixth day after continuous intrathecal drug infusions and prepared for receptor binding assays. [^{3}H]MK-801 (0.1–60 nM) was used as the radiolabelled ligand for saturation binding experiments in the presence of glycine (10 μM) and NMDA (100 μM). Unlabelled MK-801 (10 μM) was used to determine nonspecific binding. The results are expressed as mean (SEM) of at least six separate assays. Each assay was performed with three pooled spinal cords and in triplicate. *$P<0.01$ (compared with control group)

	Control	MK-801	Morphine tolerance	Morphine+MK-801
B_{max} (fmol mg^{-1})	110.5 (31.3)	121.0 (12.7)	72.2 (31.5)	105.6 (18.0)
K_D (nM)	1.50 (0.13)	1.20 (0.56)	0.41 (0.09)*	1.27 (0.91)
Hill coefficient	1.02 (0.07)	0.97 (0.04)	1.03 (0.03)	0.95 (0.06)

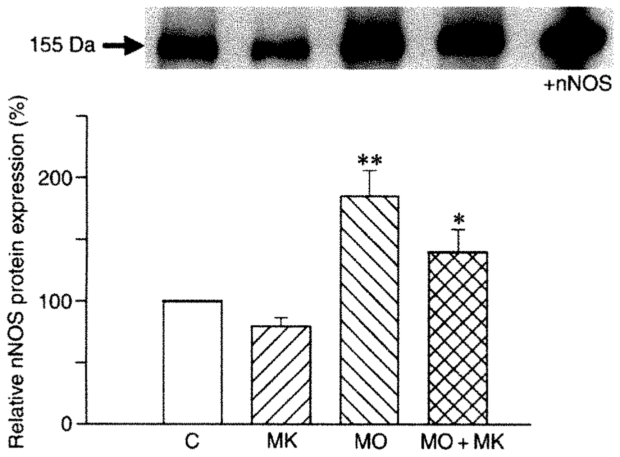

Fig 3 nNOS protein expression in the dorsal lumbosacral segments of rat spinal cords after various drug treatments, measured by western blot analysis. Rat spinal cords were obtained and treated as in Fig. 1. The dorsal lumbosacral segments of rat spinal cords were used for western blot analysis as described in Materials and methods. The 155 kDa nNOS protein band revealed by monoclonal nNOS antibody on a typical western blot are shown at the top. The positive control of nNOS (+nNOS; 1 μg) is shown in the right-most lane. The optical density of each protein band was quantified by densitometry and the relative optical density was calculated by taking the density of the control band as 100%. The mean intensity of the nNOS protein bands in the four groups is shown below. Data are expressed as mean±SEM of results from 10 rats in each group. **$P<0.01$ (control group compared with MO group), *$P<0.05$ (MO group compared with MO+MK group). C, Control (normal saline); MO, morphine; MK, MK-801; MO+MK, morphine co-administered with MK-801.

NMDA receptor channels, which is seen as a prevention of an increase in [^{3}H]MK-801 binding affinity.

Western blot analysis showed that nNOS protein expression was greater in the spinal cords of morphine-tolerant rats than in control rats, and that MK-801 prevented this up-regulation. This finding is in agreement with a previous report, and supports the involvement of nNOS, via NMDA receptor activation, in the development of morphine tolerance.[20] Many previous studies using the antisense approach, *in situ* hybridization and immunohistochemiical techniques have shown increases in mRNA level and in the activity of nNOS,[14 16] but not in iNOS in morphine-tolerant animals.[21] In our western blot study, iNOS was undetectable in the spinal cords of both control and morphine-tolerant rats. Even when we loaded 100 μg protein (20 times more than the amount of nNOS) and prolonged the time of transfer; we still could not detect iNOS. In an immunocytochemical study, Wu and colleagues[22] showed that iNOS was only distributed in the ependymal cell layer around the central canal in naive animals and was more densely stained, in the same area, after induction of arthritis. Our samples were collected from the dorsal horn of the spinal cord and did not include the central canal, which may explain why we could not detect iNOS expression. NOS inhibitors also reduce morphine tolerance.[10–13] It has been suggested that morphine tolerance leads to activation of NMDA receptors followed by the subsequent release of nitric oxide. Mayer and colleagues[23] reported that opioid tolerance was associated with NMDA receptor activation. Blockade of nitric oxide production, the consequence of NMDA receptor activation, resulted in the prevention or retardation of development of opioid tolerance.[12 24]

In conclusion, our results suggest that morphine tolerance may be associated with NMDA receptor activation and subsequent nNOS up-regulation. Inhibition of NMDA receptor activity may inhibit morphine tolerance and thus preserve the antinociceptive effect of morphine. The underlying mechanism may involve inhibition of NMDA receptor channel activity, subsequent attenuation of nNOS activity and inhibition of pain facilitation.

Acknowledgements

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Determination of succinylcholine in plasma by high-pressure liquid chromatography with electrochemical detection

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The plasma concentration of the neuromuscular blocking drug, succinylcholine, is difficult to measure. We have measured concentrations of the breakdown product of succinylcholine, choline, to assess whether choline concentration gives an accurate measure of succinylcholine concentration. Choline concentration was measured by HPLC and electrochemical detection in two blood or plasma samples, one in which succinylcholine hydrolysis was inhibited by 10^{-5} M physostigmine and another in which succinylcholine was completely hydrolysed in 20 min by 200 mU butyrylcholinesterase at 37°C. The difference in choline content between the two samples gives the succinylcholine concentration. Ninety-five per cent recovery of choline was achieved. Choline standard curves were linear from 156 pmol ml^{-1} to 200 nmol ml^{-1}. Within-day and between-day mean coefficients of variation for succinylcholine hydrolysis were small (mean (SD) 3.7% (1.2%) and 3.8% (1.6%), respectively). We conclude that this method of measuring succinylcholine concentration in blood is accurate, repeatable and relatively easy.

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Succinylcholine is a short-acting, depolarizing neuromuscular blocking agent[1] that is used extensively in anaesthesia. Its duration of action is short because it is rapidly metabolised by butyrylcholinesterase (BuChE) (EC 3.1.1.8) in plasma.[2] Effective blood concentrations of succinylcholine are difficult to determine because of its rapid hydrolysis. Succinylcholine is first hydrolysed to yield succinylmonocholine and choline. Succinylmonocholine is then broken down to choline and the inactive succinic acid[3] (Fig. 1, reaction 1). This second step shows little activity at physiological pH[4] and is likely to yield only a small amount of choline after a bolus dose of succinylcholine.[3 5]

Estimates of succinylcholine in blood and tissues have involved bioassays,[6] radiolabelled succinylcholine[7] or expensive and sophisticated ion-pair extraction followed by demethylation, gas chromatography and mass spectrometry.[8 9] These methods are costly and time-consuming and are not practical for measuring succinylcholine concentrations in plasma in pharmacokinetic studies. Most studies of this compound have, therefore, dispensed with succinylcholine plasma concentrations and rely on following the time-course of neuromuscular blockade in response to controlled infusions and/or bolus intravenous injections.[10–13]

To examine succinylcholine overdose in large animals, such as elephants,[14] we needed to measure the plasma succinylcholine concentrations as it is not practicable to assess neuromuscular blockade in these animals. We have, therefore, established a method for determining succinylcholine plasma concentrations by measuring the concentration of the succinylcholine cholinesterase reaction product, choline, instead of succinylcholine itself. Measurement of choline concentrations is easier and, as we show, gives a very accurate measure of succinylcholine concentration.

Materials and methods

Acetylcholine and choline concentrations can be determined using high-pressure liquid chromatography with electrochemical detection.[15] In the BAS acetylcholine/choline analytical kit (Bioanalytical Systems, West Lafayette, IN, USA) these compounds are separated in a reversed-phase column and then passed through an immobilized enzyme reactor containing acetylcholinesterase (AChE) (EC 3.1.1.7) and choline oxidase. In the usual application of this system for the measurement of acetylcholine, the AchE yields choline, which is then oxidized by choline oxidase (Fig. 1, reaction 2). The subsequent reaction

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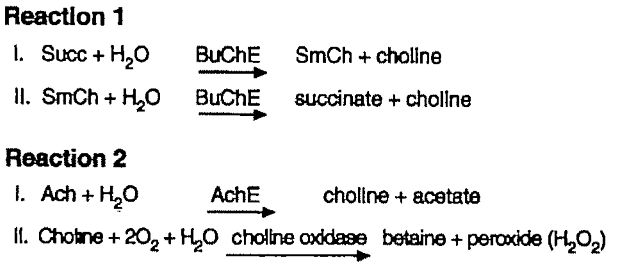
Reaction 1
I. Succ + H2O BuChE SmCh + choline
II. SmCh + H2O BuChE succinate + choline
Reaction 2
I. Ach + H2O AchE choline + acetate
II. Choline + 2O2 + H2O choline oxidase betaine + peroxide (H2O2)

Fig 1 Reaction 1. Hydrolysis of succinylcholine (Succ) by butyrylcholinesterase (BuChE). The first step yields succinylmonocholine (SmCh) and choline. SmCh is then hydrolysed to yield choline and succinate. Reaction 2: Hydrolysis of acetylcholine and choline by acetylcholinesterase (AchE) and choline oxidase, respectively, in the Bioanalytical Systems immobilized enzyme reactor (see text for details).

yields peroxide, which is detected at a platinum electrode. Although the molecular structure of succinylcholine is similar to that of acetylcholine, the highly specific enzyme AchE has no measurable activity against succinylcholine in this system,[16] so only the oxidation of choline (reaction 2, step II) is relevant to the quantification of succinylcholine. This method has been used to determine the ability of human plasma cholinesterase to hydrolyse succinylcholine.[16]

We propose that the succinylcholine concentration can be determined by hydrolysing succinylcholine in plasma and measuring the concentration of the reaction product, choline. The amount of choline already present in the plasma at that moment (endogenous choline together with any arising from prior succinylcholine hydrolysis) must be determined. To measure the pre-existing choline in a blood sample, plasma cholinesterase activity in the sample must be stopped immediately. In a duplicate, unblocked, aliquot, all the remaining succinylcholine is completely hydrolysed. The difference in choline content between these two measurements gives the succinylcholine concentration.

Chemicals

Physostigmine salicylate and sodium perchlorate were purchased from Sigma Chemical Co. (Saint Louis, MO, USA). Succinylcholine was donated by Glaxo SA (Pty) Ltd (Johannesburg, South Africa). Succinylmonocholine was prepared by the reaction of choline iodide with succinic anhydride (Sigma).[17] Choline, acetylcholine, AChE (EC 3.1.1.7) and choline oxidase (EC 1.1.3.17) were supplied in the BAS acetylcholine/choline analytical kit (MF-9053; Bioanalytical Systems). BuChE (EC 3.1.1.8; human origin; 100 U/2.1 mg) was purchased from Boehringer Mannheim Gmbh (Mannheim, Germany). Choline standards were prepared in the diluent recommended by BAS, namely 52 mM acetic acid (pH 5.5) with the antimicrobial agent Kathon (Bioanalytical Systems) at 0.01%.

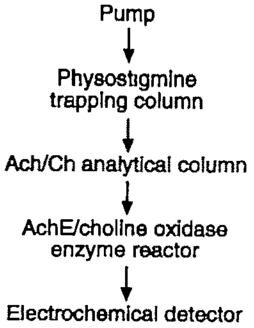
Pump
Physostigmine trapping column
Ach/Ch analytical column
AchE/choline oxidase enzyme reactor
Electrochemical detector

Fig 2 Post-column enzyme reactor and analytical column sequence. The trapping column removes physostigmine so that it does not poison the enzyme reactor

Chromatographic conditions

The chromatographic flow sequence is shown in Fig. 2. A Varian Star 9001 solvent delivery system (Varian Chromatography Systems, Sunnyvale, CA, USA) delivers mobile phase at a flow rate of 0.7 ml min^{-1}. The mobile phase was 0.05 M Tris/$NaClO_4$ (pH 8.50) with 0.5% of the antimicrobial solution Kathon (Bioanalytical Systems). A 20 µl injection loop was used and a physostigmine trapping column (MF-6262, Bioanalytical Systems) was placed before the analytical column (acetylcholine analytical column; 96.0 mm×5.0 mm i.d.; Bioanalytical Systems). Choline, which was retained in the analytical column for 11.1 min, was then passed through a 30 mm long immobilized enzyme column containing acetylcholine esterase (EC 3.1.1.7) and choline oxidase (60 U each). The reaction of the enzyme with its substrate yielded peroxide, which was measured at a platinum working electrode. The electrode potential was set at 0.5 mV relative to an Ag/AgCl reference electrode. The resulting current was monitored using an LC-4B amperometric detector (Bioanalytical Systems). Output was set at 5–20 nA full scale, depending on the concentrations measured and the electrode sensitivity. The detector output was amplified and recorded with a STAR chromatography workstation interface and software (version 4.0; Varian).

Calibration curves

Choline calibration curves were obtained by injecting serial dilutions of a 20 µM standard into the HPLC system. Similar concentrations of succinylcholine were injected into the HPLC apparatus. Calibration curves were generated by plotting the analyte peak-height against its concentration. The lower limit of quantification was defined as the lowest concentration that could be measured with a coefficient of variation (CV) of <15% for repeat determinations.

Succinylcholine hydrolysis

To establish the optimal incubation time and enzyme activity to complete the *in vitro* hydrolysis of succinylcholine, excess BuChE (20–600 mU) was incubated with 0.1 ml of succinylcholine standards (≤200 μM) in 0.5 ml of 0.05 M phosphate buffer (pH 7.4) at 37°C. Excess BuChE was also incubated with both fresh human plasma and heat-inactivated plasma (to destroy endogenous cholinesterases) under the same conditions. In these plasma standards, succinylcholine was added (≤200 μM final concentration) immediately before addition of the enzyme. After incubation for a specified time (between 5 and 120 min), the reaction was stopped by addition of 1 ml ice-cold 0.1 M perchloric acid. Samples were then centrifuged at 5000×*g* at 4°C for 5 min and stored at –70°C until analysed for choline. Samples lacking enzyme or substrate or both were also assayed to determine spontaneous non-enzymatic hydrolysis of succinylcholine and endogenous choline concentration. A separate series of samples was used to establish the appropriate concentration of enzyme inhibitor. Physostigmine, an irreversible non-specific cholinesterase inhibitor, was added to these samples at concentrations of 10^{-6}–10^{-3} M to block endogenous cholinesterase activity.

Complete hydrolysis of succinylcholine to choline and succinic acid is a two-step reaction, yielding choline at each step.[3] To confirm the previous observations that succinylmonocholine would yield little choline in our technique,[16] further plasma samples containing succinylcholine (129 μM) or succinylmonocholine (50 μM), or both, were incubated for ≤120 min with excess BuChE.

Estimation of plasma succinylcholine

To confirm that our technique can measure differences in choline content between two aliquots of a blood sample, the plasma concentration–time profile of succinylcholine was determined *in vitro*. Succinylcholine (10.5 mg) was added to 500 ml of human donor blood (haematocrit=0.46). This succinylcholine concentration would approximate a 1.5 mg kg^{-1} i.v. bolus dose for a 70 kg individual, immediately distributed in 5 litres of blood. Two 2 ml aliquots of blood were withdrawn from the pool immediately before the addition of succinylcholine and then after the addition of the succinylcholine at 30 s intervals for the first 5 min and every 2 min thereafter. One aliquot was immediately treated with physostigmine (final concentration 0.01%) to stop further hydrolysis of succinylcholine. Both samples were placed on ice-water and centrifuged within 5 min at 4°C to harvest the plasma. The choline content of each aliquot was determined in duplicate by the previously standardized procedure (i.e. incubation with 200 mU BuChE, 37°C, 20 min). The aliquot blocked with physostigmine was incubated without BuChE, while the duplicate unblocked sample was incubated with 200 mU BuChE. The activity of this added enzyme was monitored by including a 124 μM succinylcholine control sample which was assayed in duplicate with each batch of eight samples. Based on the study of succinylcholine hydrolysis, a peak representing 150 pmol choline was expected for complete hydrolysis of the control sample in 20 min. The results of the assay were discarded if the averaged control differed from the expected value by >3%. (This occurred in only one batch when the waterbath thermostat malfunctioned.)

Precision and accuracy

HPLC choline detection

Within-day precision was assessed by repeatedly injecting the same choline calibration standards into the HPLC system. Standards were prepared from serial dilutions of a 20 μM choline solution. Between-day precision was assessed by injecting the same choline calibration standards over a period of 3 weeks.

Enzyme assay

Within-assay precision was assessed using succinylcholine-spiked heat-inactivated plasma samples which were incubated with BuChE (200 mU) for 20 min at 37°C as before. HPLC assays were then completed in the same 24 h period. Between-assay precision was assessed using succinylcholine-spiked heat-inactivated plasma samples under the same assay conditions on five different days. HPLC assays were again completed on the day of each enzyme assay.

Statistics

Unpaired *t*-tests at $P<0.05$ were used to test for differences between groups.

Results

Calibration data

The peak height of the choline standard varied linearly with concentration (Table 1). Serial dilution of the 20 μM standard yielded a lower limit of quantification of 156 pmol ml^{-1} (3.12 pmol injected; signal-to-noise ratio=4). By repeated injection of a 5 nmol ml^{-1} choline standard (n=6), the CV for the chromatographic procedure was determined to be 0.55%. No peaks were detected when succinylcholine was injected.

Precision of the HPLC method of choline detection

Within-day reproducibility was determined from calibration curves prepared the same day in replicate (n=6). Between-day reproducibility was determined from calibration curves prepared on different days (n=10). The same stock solutions were used throughout. Results are given in Table 1. For each calibration curve, the slope was significantly different from zero ($P<0.05$).

Table 1 HPLC detection of choline. A 20 μM choline standard was serially diluted to generate a standard curve. Standards in the concentration range 20 nmol ml^{-1} to 625 pmol ml^{-1} were injected into the HPLC apparatus. To determine within-day reproducibility, six independent calibration curves were established in 1 day. To determine between-day reproducibility, calibration curves established on 10 different days were compared. [a]Linear unweighted regression $y=bx+c$.

	Variance of the linear regression analysis[a] **(r^2 (SD))**	**Slope (b) (Mean (SD))**	**Intercept (c) (Mean (SD))**
Within-day reproducibility (n=6)	0.9997 (1.03)$\times 10^{-4}$ (CV=0.01%)	2 (0) (CV=0%)	7.2 (0.4) (CV=5.2%)
Between-day reproducibility (n=10)	0.9996 (3.62)$\times 10^{-4}$ (CV=0.04%)	2 (0) (CV=0%)	5.9 (0.9) (CV=15.2%)

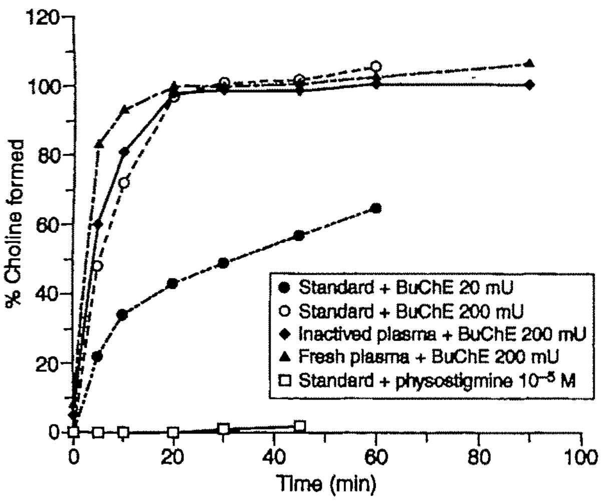

Fig 3 Amount of choline formed from succinylcholine hydrolysis (where 100% represents the amount expected from complete hydrolysis of succinylcholine in the first reaction step). A 0.1 ml sample in 0.5 ml phosphate buffer was incubated at 37°C under the following conditions: 100 μM succinylcholine standard with 20 or 200 mU BuChE, 124 nmol succinylcholine per ml of plasma with 200 mU BuChE in heat-inactivated or fresh plasma or with 10^{-5} M physostigmine.

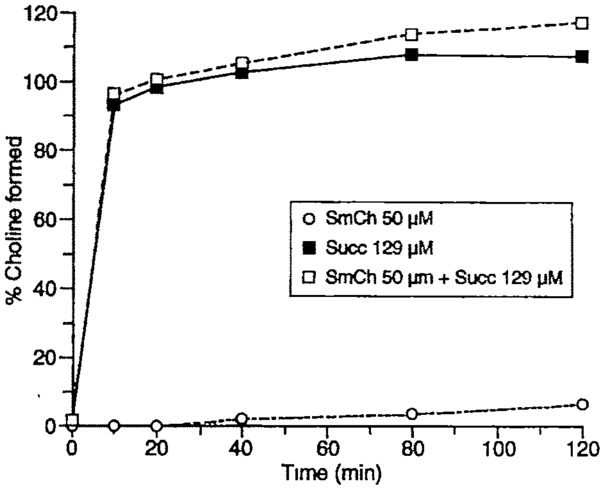

Fig 4 Amount of choline formed from succinylmonocholine (SmCh) and succinylcholine (Succ) hydrolysis (where 100% represents the amount expected from complete hydrolysis of succinylcholine in the first reaction step). A 0.1 ml fresh plasma sample in 0.5 ml 500 mM phosphate buffer was incubated with 200 mU BuChE at 37°C with succinylmonocholine at 50 μM or succinylcholine at 129 μM or both together.

Succinylcholine hydrolysis

Figure 3 shows representative data for the amount of choline produced from standards and spiked plasma samples incubated with excess BuChE. The figure shows that both standards and spiked plasma (0.1 ml) in 0.5 ml phosphate buffer require an incubation period of ≥20 min at 37°C in the presence of 200 mU BuChE to effect complete hydrolysis of succinylcholine. Increasing the amount of enzyme to 400 or 600 mU did not significantly increase the extent of hydrolysis that occurred in ≤20 min (data not shown). Figure 3 also shows that the amount of choline produced by excess BuChE in spiked plasma (succinylcholine at 124.0 nmol ml^{-1}) was not significantly different between heat-inactivated and fresh plasma (122.1 (4.0) and 124.7 (2.9) nmol ml^{-1}, respectively) after incubation for 20 min. This means that the 200 mU exogenous enzyme is sufficient to hydrolyse all the succinylcholine present, so that the contribution made by any endogenous BuChE is not essential for the assay. Also shown in this figure is the per cent hydrolysis of succinylcholine when 10^{-4} M physostigmine was present in the plasma.

Physostigmine at 10^{-9}, 10^{-6}, 10^{-5} and 10^{-4} M inhibited the endogenous enzymatic hydrolysis of succinylcholine by 4%, 55%, 89% and >99% respectively in the first 20 min. For the estimation of plasma succinylcholine, we therefore added physostigmine at 0.01% final concentration (i.e. 1.54×10^{-4} M) in the aliquots in which further succinylcholine hydrolysis was to be inhibited.

Figure 4 shows the amount of choline formed from succinylmonocholine and succinylcholine. For the reaction conditions, complete hydrolysis of the succinylcholine standard in only the first step of the reaction was expected to yield a chromatogram peak representing 150.0 pmol of choline. Complete hydrolysis of the succinylmonocholine standard was expected to yield a peak representing 58.4 pmol. Within the first 20 min, the choline produced from the combined succinylcholine+succinylmonocholine standard does not exceed that produced by the succinylcholine standard alone. Further evidence that the choline measured

Table 2 Within- and between-assay reproducibility of succinylcholine analysis The recovery of succinylcholine from plasma was estimated from the amount of choline liberated from the reaction with butyrylcholinesterase The mean recovery of succinylcholine from quintuplicate human plasma samples was used to establish the within-day assay reproducibility The mean recovery of succinylcholine from triplicate plasma samples was also completed on five different days to establish the between-assay reproducibility of the results

Theoretical concentration (nmol ml^{-1})	Within-assay reproducibility (n=5)			Between-assay reproducibility (n=5)		
	Mean (SD) experimental concentration (nmol ml^{-1})	Recovery (%)	CV (%)	Mean (SD) experimental concentration (nmol ml^{-1})	Recovery (%)	CV (%)
124.0	121.2 (3.5)	97.8	2.9	125.3 (2.3)	101.0	1.8
62.0	61.2 (1.2)	98.7	2.0	58.3 (2.7)	94.0	4.6
31.0	29.4 (1.3)	94.8	4.4	30.3 (1.8)	97.7	5.9
15.5	14.1 (0.7)	91.0	5.0	14.1 (0.4)	91.0	2.8
7.8	7.1 (0.3)	91.0	4.2	7.4 (0.3)	94.9	4.1

comes almost exclusively from the first hydrolysis reaction is contained in Table 2 (see below).

Precision of the succinylcholine assay

The within-assay reproducibility of the hydrolysis reaction for succinylcholine was determined in replicate samples (n=5) at succinylcholine concentrations ranging from 7.8 to 124.0 nmol ml^{-1} with 200 mU BuChE for 20 min. To test between-assay reproducibility, duplicate samples in the same concentration range were incubated with BuChE for 20 min on five different days over a period of 2 weeks. Results are given in Table 2. Even at the lower concentrations of succinylcholine, no more choline can be detected than is expected from only the first step of the hydrolysis reaction.

Plasma succinylcholine

Human donor blood rapidly but incompletely hydrolysed succinylcholine. Figure 5 shows the difference in choline concentration between the aliquots, expressed as the amount of succinylcholine present at that time. The volume of the donor blood was 500 ml and, at a haematocrit of 0.46, it can be assumed that 10.5 mg succinylcholine was distributed in 270 ml plasma. The expected succinylcholine plasma concentration at time zero was therefore about 98 nmol ml^{-1}. Hydrolysis appeared to be delayed over the first minute, but this was probably because of incomplete mixing of the succinylcholine in the sample. After 1 min, the mean (SD) measured succinylcholine concentration was 91.1 (0.8) nmol ml^{-1}. A linear fit from 1 to 5 min (y=–21.6x+114.8; n=18; r^2=0.9737) indicates that succinylcholine was hydrolysed at a rate of about 21.6 nmol ml^{-1} min^{-1}. Beyond 5 min it appears that there is diminished plasma cholinesterase activity, leaving about 12% of the initial dose of succinylcholine unhydrolysed after 10 min.

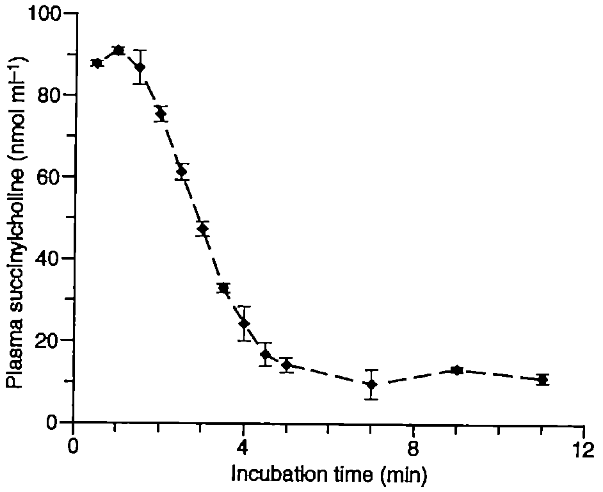

Fig 5 Concentration of succinylcholine in plasma. Succinylcholine (10.5 mg) was added to a 500 ml pool of donor blood. Duplicate aliquots were withdrawn at intervals and the plasma was assayed for choline (see text for details).

Discussion

This method for estimating plasma succinylcholine concentrations requires the complete hydrolysis of any succinylcholine remaining in the sample and the accurate measurement of choline concentration. We needed to hydrolyse succinylcholine to produce choline because the AChE (EC 3.1.1.7) in the enzyme reactor column has little activity against succinylcholine. Under our chromatographic conditions, no succinylcholine peaks could be detected. A similar result has been found by others using this Bioanalytical Systems kit.[16] This lack of succinylcholine hydrolytic activity in the enzyme column raises serious doubts concerning reports in which it has been claimed that succinylcholine concentrations in plasma have been determined directly using this Bioanalytical Systems acetylcholine/choline detection kit.[18]

In our method, it is assumed that the choline generated during the hydrolysis of succinylcholine comes only from the first step of that reaction. The kit we have used enabled us to produce consistent standard curves for choline and to measure reliably the choline content of any sample. To estimate plasma succinylcholine concentrations accurately, we needed to stop the further hydrolysis of succinylcholine in one aliquot of a blood sample, but allow hydrolysis to continue to completion in a second aliquot of the same sample. The difference in choline concentrations is a measure of succinylcholine concentration.

We found that 10^{-4} M physostigmine completely inhibits endogenous BuChE activity. Two review articles[19 20] state that 10^{-5} M physostigmine will completely inhibit BuChE activity, but our data suggest that higher concentrations are needed. For the aliquot in which complete succinylcholine hydrolysis was desired, preliminary observations indicated that relying only on the endogenous BuChE activity to accomplish this hydrolysis gave variable results. However, when 200 mU of human BuChE was incubated with the samples for 20 min, the mean accuracy of succinylcholine estimation was improved, to 95% (Table 2). The large amount of BuChE needed may appear to represent a low activity of the exogenous BuChE, but we used an incubation pH of 7.4. The optimum pH for the enzymatic hydrolysis of succinylcholine by BuChE is between 8 and 9,[4] but non-enzymatic degradation of succinylcholine at this pH is considerable.[4 16] At high pH, excess choline would thus be produced in the physostigmine-blocked aliquot, thereby reducing the accuracy of the technique.

The assumption that virtually all choline is produced from succinylcholine and that negligible hydrolysis of SmCh is occurring, is supported by our finding that recovery of choline never exceeds that expected from hydrolysis of succinylcholine (Table 2). When samples containing a 2.5:1 mixture of succinylcholine and succinylmonocholine are incubated together with BuChE, the recovery still does not differ from that expected from succinylcholine alone. Two previous studies also found that hydrolysis of succinylmonocholine is slower than that of succinylcholine.[3 5] Even more importantly, these studies concluded that the affinity of the enzyme for the succinylcholine was such that succinylmonocholine was catabolized only after almost complete hydrolysis of succinylcholine. The optimal pH for the enzymatic hydrolysis of succinylmonocholine is between 5 and 6,[4] and it is possible that only after a significant amount of choline has been generated in the *in vitro* sample (reaction 1, step I) does the pH begin to favour succinylmonocholine hydrolysis. Our assumption that the measured choline comes only from the first-step hydrolysis of succinylcholine is thus likely to be true, especially at physiological pH.

Our estimate of plasma succinylcholine concentration relies on the accurate measurement of the difference in choline content between a hydrolysed aliquot and an inhibited aliquot, so it is important to note the limitations of this estimate. One possible source of error is in the HPLC determination, which we have shown is <1%. The other source of error arises from the hydrolysis of succinylcholine in the uninhibited aliquot. The mean CV in our examination of the within-assay reproducibility is <4%, and of course includes the 1% variation in the HPLC assessment. This means that only when the choline concentration of the inhibited aliquot lies within 4% of the choline concentration of the hydrolysed sample will the accuracy of this method be compromised. Preliminary *in vivo* data have shown that, following succinylcholine administration, a difference of <5% between the hydrolysed and inhibited aliquots typically takes >8 min to develop.

We also used our technique to assess the disappearance of succinylcholine from whole blood. We know of one *in vitro* study where the amount of succinylcholine present in human blood was estimated at intervals.[6] That study showed that approximately 85% of the succinylcholine was hydrolysed within the first 30 s after mixing with blood. After 2 min, only 5% of the succinylcholine remained. The succinylcholine in that study was, however, estimated by bioassay, so lack of an effect cannot be related to absolute disappearance of the compound. A recent study used a different HPLC method to measure plasma succinylcholine concentration directly after an i.v. bolus dose in humans.[21] In that study, the clearance of succinylcholine was about 23 nmol ml^{-1} min^{-1} over the first 3 min. The net rate of succinylcholine loss we measured (21 6 nmol ml^{-1} min^{-1}) is similar.

The issue of accuracy of the assessment is relevant to the results we obtained for the *in vitro* hydrolysis of succinylcholine in donor blood. Since our data show that the minimum difference in choline concentration between the two aliquots (i.e. the succinylcholine estimate) was about 12%, this must reflect an inability of the blood to hydrolyse completely all the succinylcholine present This phenomenon has not been evident in *in vivo* studies where the intact circulation still facilitates clearance of both succinylcholine and choline from the blood.[21 22] However, in a study of succinylcholine overdose in dogs, cessation of regular heartbeats and a loss of arterial pressure after 4 min resulted in no further clearance of succinylcholine from the plasma over the following 6 min.[8] This suggests that plasma cholinesterase activity was also diminished in that study

We conclude from our results that this assay accurately detects almost all choline produced from succinylcholine and is therefore an accurate measure of succinylcholine concentration. To produce these accurate results, excess BuChE must be added to the sample to ensure conversion of succinylcholine to choline. Under these assay conditions, none of the measured choline is expected to be derived from succinylmonocholine. This technique can, therefore, be used to obtain reliable plasma succinylcholine data in humans and other mammals in a relatively easy and simple manner.

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REVIEW ARTICLE

The role of albumin in critical illness

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The last 25 yr have seen major advances in our understanding of albumin. We now know the amino acid sequences of bovine and human albumin, the complete gene sequence of human albumin, and the location of mutations in the gene sequence. During the 1990s, the heart-shaped crystalline structure of albumin has been described and a new protein, termed α-albumin (afamin), has been added to the albumin superfamily, which otherwise consists of serum albumin, vitamin D-binding protein and α-fetoprotein.[74]

The function of circulating albumin in critical illness is not fully understood. It may differ significantly from that in healthy subjects. A low serum albumin concentration in critical illness is associated with a poor outcome.[2 11 66] Despite theoretical advantages for using human albumin solution as a plasma substitute, studies have shown that correcting hypoalbuminaemia has no impact on outcome in the critically ill.[28 96 97]

This review will examine the role of serum albumin in health and critical illness. It will also review aspects of the physiology of this protein that may be expected to lead to significant dysfunction in critical illness. Finally, the case for and against the use of exogenous albumin in the management of critically ill patients will be discussed.

Structure of albumin

In humans, albumin is the most abundant plasma protein, accounting for 55–60% of the measured serum protein.[34] It consists of a single polypeptide chain of 585 amino acids with a molecular weight of 66 500 Da. The chain is characterized by having no carbohydrate moiety, a scarcity of tryptophan and methionine residues, and an abundance of charged residues, such as lysine, arginine, glutamic acid and aspartic acid.[77] The mature, circulating molecule is arranged in a series of α-helices, folded and held by 17 disulphide bridges. The folding creates subdomains of three contiguous α-helices in parallel (Fig. 1). A pair of subdomains face each other to form domains. These can be seen as cylindrical structures with polar outer walls and a hydrophobic central core.[23]

The tertiary structure of human albumin crystal has been isolated by x-ray crystallography. It is seen as a heart-shaped molecule 80 × 30 Å.[36] In solution, the shape is quite different. The three domains appear to be arranged in an ellipsoid pattern, giving the molecule low viscosity (Fig. 2).

The molecule is very flexible and changes shape readily with variations in environmental conditions and with binding of ligands.[77] Despite this, albumin has a resilient structure and will regain shape easily, owing to the disulphide bridges, which provide strength, especially in physiological conditions.[14] After their rupture, the molecule can re-establish these bridges and regain its structure. Denaturation occurs only with dramatic and non-physiological changes in temperature, pH and the ionic or chemical environment.

Albumin metabolism

The serum albumin concentration is a function of its rates of synthesis and degradation and its distribution between the intravascular and extravascular compartments. The total body albumin pool measures about 3.5–5.0 g kg^{-1} body weight (250–300 g for a healthy 70 kg adult). The plasma compartment holds about 42% of this pool, the rest being in extravascular compartments. Some of this is tissue-bound and is therefore unavailable to the circulation. Each day, 120–145 g of albumin is lost into the extravascular space. Most of this is recovered back into the circulation by lymphatic drainage. Albumin is also lost into the intestinal tract (about 1 g each day), where digestion releases amino acids and peptides, which are reabsorbed. There is minimal urinary loss of albumin in healthy subjects. Of the 70 kg of albumin that passes through the kidneys each day, only a few grams pass through the glomerular membrane. Nearly all of this is reabsorbed, and urinary loss is usually no more than 10–20 mg day^{-1}.

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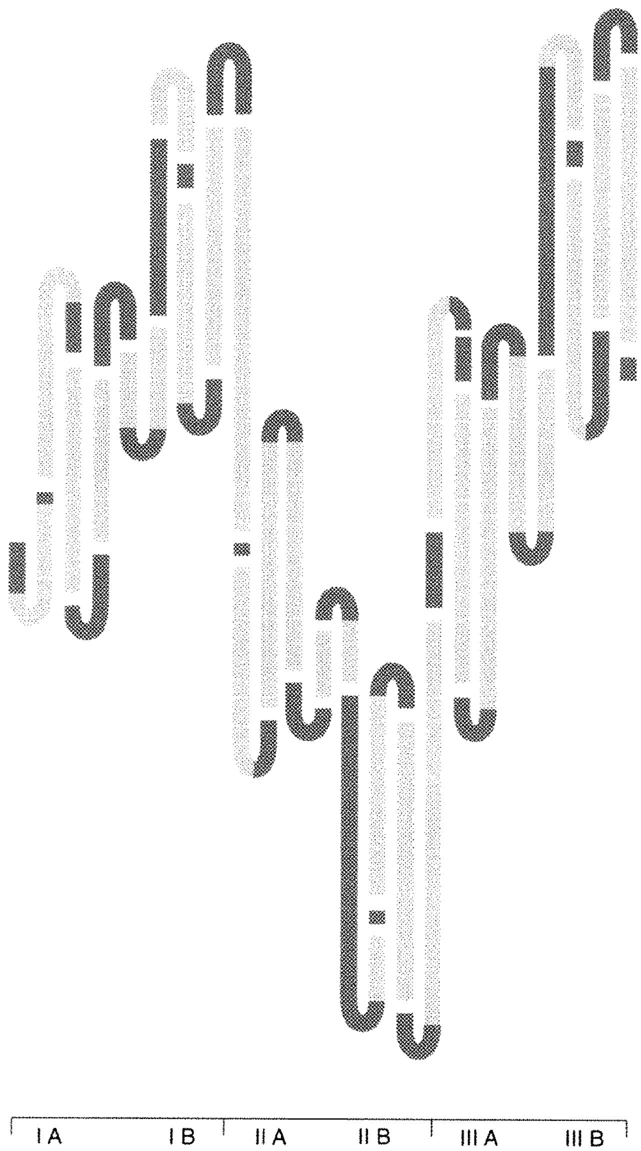

Fig 1 Two-dimensional representation of the albumin molecule reflecting the heart-shaped structure (see Fig. 2). The regions of the molecule that are normally in the α-helix configuration are shown in dark grey. The seventeen disulphide bridges are depicted in light grey. The three domains, separated into A and B subdomains, are shown along the bottom axis. Reproduced with permission from Carter and Ho, 1994.[14]

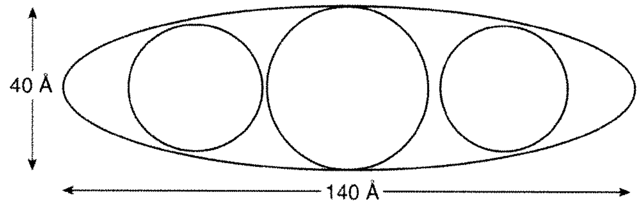

Fig 2 The ellipsoid structure of albumin in solution.[14]

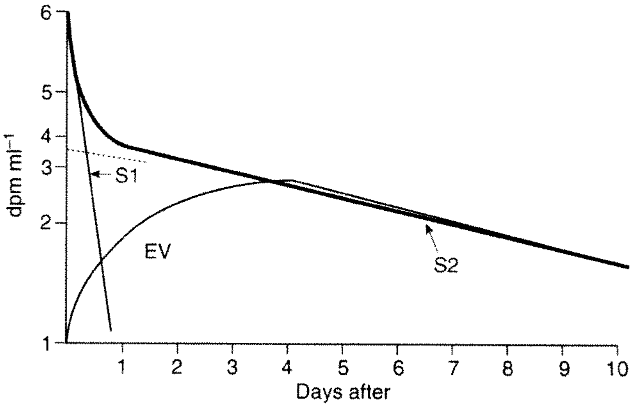

Fig 3 Decay pattern of labelled albumin versus time after i.v. injection of a tracer dose of ^{125}I-labelled human serum albumin (thick line). Slope 1 (S1) is the transcapillary escape rate, which equals about 4.5% h^{-1}. Slope 2 (S2) is the fractional degradation rate, which is about 3.7% per hour. EV is the calculated increase in extravascular labelled albumin concentration. Note that the activity of extravascular albumin is greater than that of intravascular albumin from about day 3 onwards. This suggests that degradation occurs directly from the vascular compartment. Reproduced with permission from Peters, 1996.[76]

The distribution of albumin between body compartments can be examined by injecting radiolabelled albumin into the venous circulation. A typical biexponential plot of log plasma concentration versus time shows a first-order process (Fig. 3). A two-compartment model can be constructed. There is a rapid phase of disappearance from the plasma over the first 2 days. This represents the transcapillary exchange rate of 4.5% h^{-1}, giving a distribution half-time of about 15 h. Then there is a slower exponential decay, representing the fractional degradation rate (FDR), of about 3.7% day^{-1} with an elimination half time of about 19 days. The FDR closely parallels the rate of synthesis in steady state (3.8% day^{-1}).

The extravascular pool is divided into exchangeable and remote components (Fig. 4). Significant locations of this large extravascular pool are listed in Table 1.

The mechanism of the escape of albumin into the extravascular compartment has come under review recently. Albumin must cross capillaries. Most organs in the body have continuous capillaries, but in some there are wide-open sinusoids (liver, bone marrow) or fenestrated capillaries (small intestine, pancreas, adrenal glands). Starling's theory holds that the rate of escape depends on the permeability of the wall and hydrostatic and oncotic pressures on either side of the wall.[29] Half of the escaping albumin does so through the continuous capillaries, and there appears to be an active transport mechanism to facilitate this.[76] Albumin binds to a surface receptor called albondin, which is widely distributed in many capillary beds, except in the brain.[90] [91] Bound albumin enters vesicles within the endothelial cell and is discharged on the interstitial side within 15 s. The rate of transfer is increased with the addition of long-chain fatty acids (LCFAs) to albumin, and with the cationization and glycosylation of the molecule.[76]

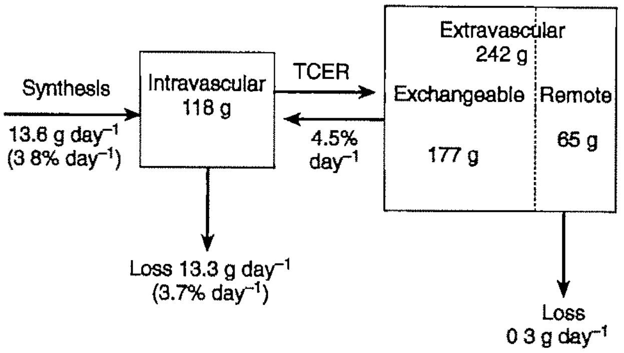

Fig 4 Typical albumin distribution in a healthy 70 kg adult. Reproduced with permission from Peters, 1996.[76]

Table 1 Distribution of extravascular albumin in the body[76]

Organ	Fraction of body weight (%)	Fraction of total extravascular albumin (%)
Skin	18.0	41
Muscle	45.5	40
Gut	2.8	7
Liver	4.1	3
Subcutaneous, etc	8	9

Table 2 Factors that modify albumin metabolism (see text for details)

Reduced albumin synthesis	
Decreased gene transcription	Trauma, sepsis (cytokines) Hepatic disease Diabetes Decreased growth hormone Decreased corticosteroids (*in vitro*)
Ribosome disaggregation	Fasting, especially protein depletion

Synthesis

In humans, albumin synthesis takes place only in the liver.[56 60] Albumin is not stored by the liver but is secreted into the portal circulation as soon as it is manufactured. In healthy young adults, the rate of synthesis is 194 (SD 37) mg kg^{-1} day^{-1}, or about 12–25 g of albumin per day.[76] The rate of synthesis rate varies with nutritional and disease states. The liver can increase albumin synthesis to only 2–2.7 times normal because most of the liver's synthetic machinery is already devoted to albumin at rest.[76] The synthetic pathway is common to eukaryotes and is also used for synthesis of other proteins.[62]

Albumin will be synthesized only in a suitable nutritional, hormonal and osmotic environment. The colloid osmotic pressure (COP) of the interstitial fluid bathing the hepatocyte is the most important regulator of albumin synthesis.[70 85 107] Synthesis requires:

- mRNA for translation;
- an adequate supply of amino acids, activated by binding to tRNA;
- ribosomal machinery for assembly;
- energy in the form of ATP and/or GTP.

The mRNA concentration available for action on ribosomes is an important factor controlling the rate of albumin synthesis. Trauma and disease processes will affect the mRNA content.[55 64] A reduction in albumin mRNA concentration, caused by a decrease in gene transcription, is seen in the acute-phase reaction mediated by cytokines, mainly interleukin-6 (IL-6) and tumour necrosis factor α (TNF-α).[12 15 72] A decrease in gene transcription is also seen in hepatoma cells and in hepatocytes damaged with carbon tetrachloride.[76]

The hormonal environment can affect the mRNA concentration. Insulin is required for adequate albumin synthesis. Diabetic subjects have a decreased synthetic rate, which improves with insulin infusion.[20] Perfused livers of diabetic rats have a 50% decrease in gene transcription.[55] Corticosteroids have complex effects on albumin synthesis. There is increased albumin synthesis with combinations of steroids and insulin, and of steroids with amino acids.[40 76] Hydrocortisone and dexamethasone both increase gene transcription *in vitro*,[65 67] but the overall *in vivo* effects are complex. Steroids also increase albumin catabolism. Growth hormone has been shown to stimulate gene transcription in cultured hepatocytes.[41]

The rate of synthesis depends on nutritional intake, more so than for other hepatic proteins[76] Fasting reduces albumin production, but specifically omitting protein from the diet causes a greater reduction in synthesis. Early in protein deprivation, there is rapid disaggregation of free and bound polysomes, which can be reversed rapidly by refeeding the subject with amino acids.[21] Two amino acids are particularly effective, tryptophan and ornithine.[83] Ornithine, unlike tryptophan, is not incorporated into albumin. It is a product of the urea cycle and acts as a precursor of the polyamine spermine. The increases in polysome aggregation and albumin synthesis with ornithine refeeding suggest that the urea cycle plays more of a role in protein metabolism than mere waste disposal.[69] Protein deprivation for a longer time leads to a 50–60% decrease in the activity and concentration of the mRNA, presumably through increased breakdown, as gene transcription is not slowed in rats on a 0–4% protein diet.[86]

Calories are important, however. There is a reduction in synthesis in starved rats, and polysomes will reaggregate with glucose feeding alone.[80] Energy rather than the amino acid supply may be more important in determining polysome aggregation under normal circumstances[23] Table 2 summarizes factors known to alter albumin synthesis.

Degradation

Total daily albumin degradation in a 70 kg adult is around 14 g day^{-1} or 5% of daily whole-body protein turnover. Albumin is broken down in most organs of the body Muscle and skin break down 40–60% of a dose of labelled albumin.[108] The liver, despite its high rate of protein metabolism, degrades 15% or less of the total. The kidneys are responsible for about 10%, while another 10% leaks through the stomach wall into the gastrointestinal tract.

The mechanism of breakdown involves uptake into endocytotic vesicles, which fuse with lysosomes in endothelial cells. This may involve binding to endothelial surface membrane scavenger receptors, called gp18 and gp30, which are widespread in the body tissues.[89] They bind altered or denatured albumin, and it is likely that chemical modification of the circulating albumin is a signal for receptor-linked lysosomal degradation. It is also possible that modification prevents degradation. Binding of LCFAs to albumin seems to protect the molecule from breakdown. In analbuminaemia, the LCFA/albumin ratio is increased and degradation is suppressed.[76] The final breakdown products are free amino acids that add to the pools of amino acids within cells and in the plasma.

Albumin and critical illness

Critical illness alters the distribution of albumin between the intravascular and extravascular compartments. There are also changes in the rates of synthesis and degradation of the protein. The serum albumin concentration will decrease, often dramatically, from early in the course of a critical illness. It will not increase again until the recovery phase of the illness. The kinetics of albumin given i.v. will differ greatly between critically ill patients and healthy subjects. The implication of this, given the important functions albumin has in health, is that using exogenous albumin to increase the intravascular albumin concentration during critical illness is beneficial. But studies have failed to show any benefit of albumin over other colloidal therapies in adults.

The altered distribution in critical illness is related to an increase in capillary leakage.[26] This occurs in sepsis[26] and after major surgical stress.[39 99] It involves dysfunction of the endothelial barrier, resulting in capillary leakage and loss of protein, inflammatory cells and large volumes of fluid into the interstitial space. The precise mediators of this capillary leakage are still being discovered and currently include:

- endotoxin from Gram-negative bacteria;[3 71]
- cytokines—TNF-α and IL-6;[12 15]
- arachidonic acid metabolites—leukotrienes and prostaglandins;[10 31]
- complement components C3a and C5a;[31]
- other vasoactive peptides—bradykinin, histamine;[71]
- chemokines—macrophage inflammatory protein 1α.[95]

The normal transcapillary escape rate for albumin increases by up to 300% in patients with septic shock, and by 100% after cardiac surgery.[26] In septic patients, the transcapillary exchange rate may well improve with appropriate treatment. With increased flow of albumin across capillary membranes, there should be an increase in lymphatic return to the intravascular compartment. Studies of albumin kinetics during major surgery have shown a reduction in the flow rate of lymph and the albumin concentration in lymph.[38] It is not known if this extends into the postoperative period. Measurement of total circulating and total exchangeable albumin pools shows a 30% reduction with major surgery,[38] consistent with sequestration of albumin into non-exchangeable sites, such as wounds, the intestine and extra-abdominal sites.[65]

The rate of albumin synthesis may be significantly altered in the critically ill.[27] In the acute-phase response to trauma, inflammation or sepsis, there is an increase in the gene transcription rate for the positive acute-phase proteins such as C-reactive protein, and decreases in the rate of transcription of albumin mRNA and the synthesis of albumin.[64] IL-6 and TNF-α both act to reduce gene transcription.[12 15] Induced inflammation in rats decreased the concentration of albumin mRNA and the rate of albumin synthesis, which reached a minimum by about 36 h and then began to rise again.[54 92] A sustained inflammatory response in critical illness may lead to prolonged inhibition of albumin synthesis.

Catabolism of albumin may also be altered. The FDR is mass-dependent. That is, as the serum albumin concentration decreases, so does the FDR. Studies have shown a significantly shorter plasma half-life in hypoalbuminaemic patients on total parenteral nutrition (9 days), but with a catabolic rate similar to normal.[94] However, in situations of increased transcapillary albumin flux, an increase in the FDR has been observed.[85] It is possible that the vascular endothelium has an important role in the degradation of albumin. In animal experiments, the tissues most actively involved in albumin catabolism are those with fenestrated or discontinuous capillaries.[108] It may be that a high rate of tissue exposure in situations of increased capillary permeability may increase catabolism. However, studies of albumin extravasation in myxoedema found that, while there was an increase in the extravascular pool of albumin, there was a decrease in the catabolic rate, implying tissue exposure and trapping of albumin, protecting it from degradation.[84]

Functions of albumin

Albumin has extensively studied and well-established physiological functions in health. There are, however, few studies on the function of albumin in the critically ill.

Oncotic pressure

In healthy subjects, the role of albumin in the maintenance of normal COP is well recognized, but there appears to be little correlation between albumin and COP in the critically ill.[35] In health, albumin contributes up to 80% of the normal COP of about 25 mmHg.[34 101 106] This is because of its high molecular weight and concentration in plasma. Albumin is present at a higher concentration than other plasma proteins, and though its molecular weight of 66.5 kDa is less than the average for serum globulins (about 147 kDa), it still has the greatest osmotic significance. This direct osmotic effect provides 60% of the oncotic pressure of albumin. The remaining 40% is a result of its negative charge, providing an attractive force for the intravascular retention of positively charged solute particles (the Gibbs–Donnan effect). Due to the large extravascular pool of albumin, its water-solubility and its negative charge, albumin also plays a significant role in the regulation of tissue fluid distribution.

Critically ill patients have a lowered serum COP. A sequential series of 200 critically ill patients had an mean COP of 19.1 mmHg.[106] A lowered COP is associated with increased morbidity and mortality in critically ill patients.[63 100 106] A serum COP of 15 mmHg was associated with a survival rate of 50%.[100] Proponents of albumin supplementation argue that giving albumin will increase the COP and avoid potentially fatal complications such as pulmonary oedema, though the association with fatal progression of respiratory failure[63] has not been substantiated by other studies. The pulmonary lymphatic system is capable of a sevenfold increase in flow rate in response to isobaric reduction in COP, to a level sufficient to induce massive peripheral oedema and ascites in baboons.[109] There is evidence to suggest that the pulmonary dysfunction in critically ill, septic patients is independent of COP.[52]

Binding of substances to albumin

The structure of the albumin molecule is such that it can incorporate many different substances. It is a flexible molecule, and bound compounds can be buried within the structure. Some general trends have emerged from binding studies. Most strongly bound are medium-sized hydrophobic organic anions, including long-chain fatty acids, bilirubin and haematin. Less hydrophobic and smaller substances can be bound specifically but with lower affinity, such as ascorbate and tryptophan. The chirality of the compound may be important: L-tryptophan is bound more strongly than D-tryptophan.[75] Monovalent cations do not bind, but divalent cations do, namely calcium and magnesium. Albumin has a strong negative charge, but there is little correlation between the charge of the compound and the degree of binding to albumin.[51] Acidic drugs tend to bind to other plasma proteins such as α1-acid glycoprotein whereas basic drugs tend to bind to albumin. There are exceptions, and drugs may bind to both.

Other endogenous compounds that bind to albumin include bile acids, eicosanoids, copper, zinc, folate and aquacobalamin. Albumin is also a secondary or tertiary carrier for some substances that have specific binding proteins, for example, steroids, including derivatives such as vitamin D and thyroxine. This can be clinically significant. Steroids have a low binding affinity for albumin but there is a large capacity owing to the high concentration of albumin.[75] Thus a significant amount may be carried by albumin, and the lower binding affinity means that there is easy off-loading at target sites.

Drug-binding studies have traditionally been performed *in vitro*, measuring affinity and competition between ligands, at non-physiological temperature and with non-human albumin species. It is difficult to draw conclusions about *in vivo* binding from these studies. In recent years techniques such as DNA sequencing, fluorescence emission of 'reporter' compounds, which respond to the presence of ligands, x-ray diffraction and the isolation of functional fragments of albumin have given insight into the functional sites of binding.[75]

Drug binding strongly affects the delivery of bound drug to tissue sites and the metabolism and elimination of the drug. The free serum concentration is the relevant factor in these processes. Highly bound drugs have only a small percentage of the total serum concentration in the free form. Other factors that are important in drug–albumin interactions and may be responsible for the wide interindividual variation seen include age (binding may decrease at the extremes); temperature, pH and ionic strength, which can affect the number of binding sites *in vitro*; and competition between drugs for binding sites.[51]

Displacement of drugs from their binding sites by other drugs or by endogenous substances occurs and may alter the distribution, pharmacological action, metabolism and excretion of the displaced drug. There are a variety of binding sites on the albumin molecule. Sudlow *et al*[98] have classified drugs into two groups according to two broad binding sites, site I and site II. Site I appears to lie along the long loop of subdomain IIa, extending into the shorter loop.[75] Many different drugs seem to bind here, including salicylates, warfarin, phenylbutazone, indometacin, digitoxin, furosemide, phenytoin, chlorpropamide and some penicillins.[75] Dyes such as sulfobromophthalein, iophenoxate (a radio-opaque dye), methyl red, Evans blue and bromocresol green also bind here, as do endogenous compounds such as bilirubin.

Site II is a hydrophobic pocket of residues located in subdomain IIIa.[14] It is responsible for binding compounds such as L-tryptophan, thyroxine (which may also bind at site I), medium-chain fatty acids and chloride. Drugs that bind here include diazepam and other 2,3-benzodiazepines, non-steroidal anti-inflammatory agents that have ionized carboxyl groups (such as ibuprofen and naproxen) and clofibrate. Many other substances bind to various different sites on the albumin molecule.

There are many factors influencing drug–albumin interactions that become relevant in critically ill patients. Renal failure provides a good example of the mechanisms involved. The serum albumin concentration may be directly altered, due to increased loss of albumin through damaged glomeruli. Renal failure may influence drug binding to albumin.[1] Possible mechanisms involved include changes in pH[19] and the accumulation of compounds which compete with drugs for binding sites. Thus, there may be an increase in the free fraction of drugs in renal failure, resulting in an increased drug effect. We have compared cyclosporin (not bound to albumin) with tacrolimus (bound to albumin) in patients after liver transplantation who were given human albumin solution to maintain a serum albumin concentration of >20 g litre^{-1} or a gelatin solution.[102] Patients given tacrolimus with the gelatin solution had a greater increase in their serum creatinine than all the other groups. The reason for this may be the greater free fraction of tacrolimus, causing nephrotoxicity. Reves and colleagues[82] showed that the onset of sleep in patients given midazolam was faster in those with a lower serum albumin concentration. We have shown that the rate of metabolism of midazolam by human liver microsomes is inversely proportional to the albumin concentration in the incubate, although the reverse occurred when human hepatocytes in long-term primary culture were used (unpublished observation, Park GA, Mller L).

Measurement of the free fraction of a drug such as midazolam *in vivo* is difficult. Patients with renal failure in an intensive care unit commonly require renal replacement therapy in the form of continuous venovenous haemofiltration. This uses a semipermeable membrane with a pore size of 45 000 Da. Substances of small molecular weight, such as midazolam, have a sieving coefficient of 1; they are freely filtered. The concentration in the filtrate will be the same as the free plasma concentration. Simultaneous measurement of blood and filtrate concentrations might allow the bound and free midazolam to be calculated (bound=total midazolam–free midazolam).

A thorough knowledge of the pharmacokinetic principles outlined above, and of possible drug interactions and displacement reactions, is vital for the management of critically ill patients. In many cases it is necessary to monitor the free serum concentrations of drugs to avoid toxicity.

Metabolic function

Apart from its vital role in transporting drugs and endogenous compounds, albumin is also involved in the inactivation of a small group of compounds.[76] Disulfiram is inactivated by binding with albumin. Members of the penem group of antibiotics bind irreversibly to albumin, through acetylation of an ε-lysine group close to the surface of the molecule in the region of Sudlow site 1.[75] The resulting complex may be clinically significant. Penicillin allergy has been linked to irreversible coupling of penicilloyl groups to these lysine groups. Coupling causes 'bisalbuminaemia', seen as a more rapidly moving albumin on an electrophoretic strip. This is associated with the appearance of antibodies to the drug–albumin complex (antipenicilloyl antibodies) in patients treated with penicillin.[53]

Albumin is also involved in the metabolism of endogenous substances such as lipids and eicosanoids, because of the avidity with which these compounds bind to albumin. For instance, lipoprotein lipase activity in adipose tissue can be stimulated by the avidity with which fatty acids, freed from lipids in fat stores, bind to available albumin. Albumin can stabilize some eicosanoids during metabolism, such as prostaglandin I_2 and thromboxane A_2; it can increase the release of arachidonate from macrophages; and it seems to favour lipo-oxygenase over cyclo-oxygenase activity.[76]

Acid–base function

The presence of many charged residues on the albumin molecule and the relative abundance of albumin in plasma mean that it can act as an effective plasma buffer.[23] At physiological pH, albumin has a net charge of negative 19. It is responsible for about half of the normal anion gap. A reduction in plasma protein concentration causes metabolic alkalosis. A decrease in serum albumin of 1 g dl^{-1} may increase standard bicarbonate by 3.4 mmol litre^{-1}, produce a base excess of 3.7 mmol litre^{-1} and reduce the anion gap by 3 mmol litre^{-1}.[58]

Antioxidant function

Under physiological conditions, albumin may have significant antioxidant potential. It is involved in the scavenging of oxygen free radicals, which have been implicated in the pathogenesis of inflammatory diseases. Physiological solutions of human serum albumin have been shown to inhibit the production of oxygen free radicals by polymorphonuclear leukocytes.[37] This may be related to the abundance of sulfhydryl (-SH) groups on the albumin molecule. These are important scavengers of oxidizing agents, such as hypochlorous acid (HOCl) formed from the enzyme myeloperoxidase, which is released by activated neutrophils.[38 103] Other plasma substances, such as uric acid and ascorbic acid, are less important scavengers, but may be more important in extracellular fluids that have a low albumin concentration.[39] The implication of this is that hypoalbuminaemic patients have a reduced potential for oxygen radical scavenging. Serum from patients with rheumatoid arthritis shows decreased protection against α1-antiproteinase inactivation by HOCl and H_2O_2.[105] The situation in critically ill patients has not been investigated.

Maintaining microvascular integrity

It is possible that albumin has a role in limiting the leakage from capillary beds during stress-induced increases in capillary permeability.[22] Endothelial cells seem to be able to control the permeability properties of the capillary membrane, possibly by altering the nature and distribution of glycoproteins in the vessel wall. Albumin plays a part in this action, though the exact mechanism is not clear. It may involve the strong negative charge on the albumin molecule repelling other negatively charged molecules in the membrane, or it may be a space-occupying function of the albumin molecule that reduces the size of channels. It is likely that only a small amount of albumin is necessary for this function. A direct protective function of albumin is suggested by the observation that albumin prevents apoptosis in cultured endothelial cells.[110] Peak protection was seen at physiological concentrations of albumin.

It is also likely that other colloids are effective in preserving microvascular architecture.[101] Medium molecular weight starches have been shown to produce higher reflection coefficients and less transcapillary leakage in animal studies, when compared with crystalloid, albumin and starches of smaller molecular weight. Human studies are needed, especially in the light of encouraging evidence of the beneficial effects of hydroxyethyl starch (HES) over albumin in terms of cardiorespiratory variables and splanchnic perfusion,[9] which suggest attenuation of endothelial cell activation, and improved intravascular volume that is possibly caused by the plugging of capillary channels.

Albumin is the most important source of sulfhydryl groups in the circulation. Nitric oxide (NO) binds to these sulfhydryl groups to form a stable S-nitrosothiol group, and is thus protected from rapid degradation. The effects of albumin on the vasodilatory properties of NO have been studied *in vitro*.[46 47] Albumin slowed the onset and reduced the maximal intensity of the vasodilatory response to NO. It is possible that albumin has a role in the modulation of vascular tone in different vascular beds, though there is no evidence for this.

Anticoagulant effects

Albumin has effects on blood coagulation. It seems to exert a heparin-like action, perhaps related to a similarity in the structures of the two molecules. Heparin has negatively charged sulphate groups that bind to positively charged groups on antithrombin III, thus exerting an anticoagulant effect. Serum albumin has many negatively charged groups. There is a negative correlation between albumin concentration and the heparin requirement in patients undergoing haemodialysis.[42] These investigations have shown a heparin-like activity of albumin, through enhancement of the neutralization of factor Xa by antithrombin III. They suggest that the hypercoagulable state seen in the nephrotic syndrome may, in part, be explained by the accompanying hypoalbuminaemia. This may also be related to the lack of the inhibitory effect of albumin on platelet aggregation. Such an inhibitory effect is both dependent on and independent of the cyclo-oxygenase system.[43]

Genetic mutations and analbuminaemia

Around 100 variant forms of the albumin molecule have been described. These have been based on electrophoretic mobility studies. The locations of about 60% of these genetic mutations are known. Besides haemoglobin, albumin has the greatest number of known variants. Only one variant has been shown to change the function of albumin. This is the form of albumin which has increased affinity for thyroxine, leading to the condition of familial dysalbuminaemic hyperthyroidism.[72]

Since the first report, in 1954, of a patient with no detectable albumin on electrophoretic studies, nearly 30 cases of analbuminaemia have been found.[73] It is a rare condition and cases are widely dispersed. This would suggest that the cause is local gene mutation. The mutant gene in a family would be expressed only through intermarriage of its descendants, resulting in a homozygous individual. The albumin gene appears to be present, but mutations produce effects such as mRNA splicing errors, and early prevention of translation by premature stop codons.[73]

The condition has baffled scientists convinced of the requirement of albumin for survival. There is some circulating albumin, probably owing to gene leakage, and cases are now defined as having a serum albumin concentration of <1 g $litre^{-1}$. This small amount of albumin seems to be sufficient for existence under normal conditions but, given a stressful environment, animal studies suggest that subsistence requires a higher circulating albumin concentration. Cases are not usually picked up until adulthood. The main pathological features are: peripheral oedema; lipodystrophy giving lower limb obesity; fatigue, and hyperlipidaemia, but without resultant atherosclerosis. Haemodynamic changes are minimal. There is a reduction in COP (16 *vs* 25 mmHg), a reduction in arterial pressure and a resultant increase in renin and aldosterone concentrations. The body seems to compensate by slowing the rate of degradation of the small amount of albumin present[73] Study of these individuals may give insight into the effects of hypoalbuminaemia in the critically ill.

The prognostic value of serum albumin

Serum albumin appears to be a reliable prognostic indicator in various contexts. A recent review suggests that serum albumin could be an independent predictor of mortality in a wide range of clinical and research settings.[32] It reports an estimated increase in the odds of death from 24 to 56% for each 2.5 g $litre^{-1}$ decrease in serum albumin concentration over the range of studies reviewed. Large community-based studies have shown a link between low serum albumin and an increase in morbidity and mortality.[49 78] Albumin concentrations may be a marker for subclinical disease in elderly patients. In studies of hospitalized patients, hypoalbuminaemia is associated with increased length of stay, higher complication rates and higher mortality.[25 93] In one study, a serum albumin concentration of less than 34 g $litre^{-1}$ was associated with a 30-day mortality rate of 24.6%. This increased to 62% if the serum albumin concentration was 20 g $litre^{-1}$ or less.[81]

The prognostic value of serum albumin extends to critically ill patients.[2 11 16 33] A low serum albumin concentration correlates with increased length of stay in the intensive care unit (ICU) and with complication rates, such as ventilator dependency and the development of new infection.[66] The daily trend of serum albumin can be a useful tool in predicting the weaning capability of patients needing mechanical ventilation.[88]

Non-survivors of critical illness have lower serum albumin concentrations than survivors,[33 90] In one study, non-survivors had lower serum albumin concentrations on admission to the ICU, and their albumin concentrations decreased more rapidly in the first 24–48 h.[59] The albumin concentration on admission was not a sensitive indicator of outcome, but the value at 24–48 h was as accurate as the APACHE II score in predicting mortality. The APACHE II system does not include serum albumin concentration as an independent predictor, and it has been found to be poorly predictive in hypoalbuminaemia.[79] The APACHE III system does include serum albumin concentration, and it is more predictive of mortality in critical illness.[50]

We have also shown a significant difference between serum albumin concentrations of non-survivors and survivors of prolonged critical illness. Patients who were in the ICU for 7 days or more and survived had higher mean serum albumin concentrations than non-survivors, and were able to recover to a higher mean serum albumin concentration than non-survivors.[6] Significantly, there was no difference between the COPs of the two groups.

Similar results have been reported in other studies, in which serum albumin was used as a measure of the nutritional state of patients.[11 16 66] Some claim a benefit in supplementing total parenteral nutrition with albumin in terms of reducing in-hospital morbidity.[13 45] However, it is now accepted that serum albumin is not a reliable marker of nutritional status in critically ill patients.[49]

Intravenous albumin: use and abuse

Albumin therapy has certain specific indications, but for volume therapy in critically ill patients no benefit over other colloidal therapies has been shown.[96 97] Stockwell and colleagues[97] examined 475 intensive care patients randomized to receive either 4.5% human albumin solution or 3.5% polygeline (Haemaccel, Aventis, Marburg, Germany) for i.v. volume replacement during their stay in the ICU. Outcome measures were length of ICU stay and mortality. All patients received crystalloid solutions for basal fluid requirements, total parenteral nutrition if enteral nutrition was not possible, and blood products as required. Some patients in the gelatin group did receive concentrated albumin if they had profound hypoalbuminaemia that was felt to be contributing to peripheral and or pulmonary oedema. The authors point out that the clinical impact of this practice was minimal, the effect on the plasma albumin concentration was short-lived and the clinical course of the patients was not altered. The practice diminished during the study. There was no difference between the two groups in length of stay or mortality, a result that surprised the authors, who outlined several potential advantages of albumin in the critically ill. The same authors also looked at pathophysiological variables in the same patients.[96] They found that patients in the gelatin group had lower mean serum albumin concentrations. When both groups were divided into survivors and non-survivors, albumin therapy maintained the serum albumin concentration in the survivors but not in the non-survivors. There was no difference between the groups in the incidence of pulmonary oedema or acute renal failure. These data are useful in confronting supposed indications for treating hypoalbuminaemia in critically ill patients. Despite improving the serum albumin concentration, there is no benefit in outcome for patients treated with albumin.

Another randomized controlled trial examined cardiorespiratory and circulatory variables in ICU patients treated with either human albumin therapy (HA) or HES.[7 9] There was no significant difference between the two groups in the haemodynamic variables studied, though the cardiac index was higher in the HES group. Long-term infusion of HES compared with HA produced improved systemic haemodynamic variables, and specifically improved splanchnic perfusion. These authors also investigated the effects of both volume therapies on plasma concentrations of markers of the inflammatory response.[8] They measured plasma concentrations of adhesion molecules, which are significantly increased during sepsis and indicate endothelial activation or damage. They found that in patients on long-term HES therapy the concentrations of adhesion molecules were unchanged or decreased, whereas in the HA group concentrations were increased, suggesting that the septic process continued or worsened in patients treated with albumin, whereas patients given HES got better, possibly because of improved microcirculatory haemodynamics.

Burnt patients are a specific group for whom albumin may have a beneficial role. In the first 24 h there is a marked increase in capillary permeability and transcapillary fluid shifts. It is argued that colloid infusion is unjustified in this situation, as it is inefficient in reducing fluid shift and may contribute to delayed pulmonary oedema.[57] However, albumin is justified after 24 h in profoundly hypoalbuminaemic patients, as it favours the reabsorption of oedema.[57] The Guidelines of the Consensus Conference in Paris have stated that albumin is not necessary for burns covering less than 15% of the body surface, but is essential from the start of treatment for patients with greater than 50% burns.[87] Between these values, albumin is required but can be postponed for up to 24 h.

Another group who may benefit from albumin therapy are cirrhotic patients with ascites requiring paracentesis. Postparacentesis circulatory dysfunction, defined as an increase in plasma renin activity on the sixth day after paracentesis, is associated with increased morbidity and mortality. Albumin was shown to be more effective than either dextran or polygeline in preventing this complication in 289 patients studied.[30] Data discussed in the following section outline further groups of patients who may benefit from albumin.

Like any therapy, albumin has its side-effects. Injudicious use can lead to fluid overload, as plasma volume increases linearly with the dose of albumin. It may cause myocardial depression, perhaps related to the binding of calcium ions.[24] Allergic reactions to albumin are rare but may occur, usually to contaminants in the solution or to polymers that form upon storage.[24] Hypersensitivity reactions may be seen when certain drugs covalently bind to albumin; penicilloyl coupling has already been mentioned. Viral transmission is highly unlikely due to prolonged heat treatment during preparation.[103] However, it is under renewed scrutiny after the decision to stop the pooling of British donated blood for manufacturing blood products, including human albumin solution, due to the theoretical risk of transmitting new variant Creutzfeldt–Jakob disease.

Albumin is expensive. A 500 ml bottle of 4.5% human albumin solution costs up to 10 times as much as a 4% gelatin solution. Considering the amount of plasma expanders required in critically ill patients, the use of albumin represents a significant cost.

Cochrane database meta-analysis

The debate about the use of albumin in the critically ill has been stimulated by the publication of a meta-analysis in the *British Medical Journal.*[17] The authors reviewed 32 randomized controlled trials, published between 1975 and 1998, in which albumin was used in the treatment of hypovolaemic, burnt or hypoalbuminaemic patients. The data suggested that the use of albumin in these groups resulted in six additional deaths per 100 patients. This message was widely broadcast by newspaper and television media, and there was a series of vigorous responses to this article from the medical fraternity. The controversy seems to have centred on the validity of the conclusions drawn from such a heterogeneous group of studies. The tool of meta-analysis is relatively new in statistical terms. In the current era of evidence-based medicine, clinicians are right to be wary of data re-examined by an alien tool. To change current clinical practice, evidence must be unequivocal and widely accepted. This systematic review did not present new data, and it is correct to criticize conclusions about mortality data from studies not using it as an outcome measure. However, the authors have clearly discussed the limitations of the review, acknowledging that the studies were small and there were few deaths. The choice of mortality as the outcome measure of the meta-analysis was based on the availability in the studies of data on death, and the measurement error and bias that may be associated with using pathophysiological outcomes. They point out that the studies examined represent the current licensed indications for albumin, which are the emergency management of shock, the treatment of burns, and conditions associated with hypoproteinaemia. They also acknowledge the possibility of publication bias threatening the validity of the meta-analysis, but are in a position to use sophisticated statistical analysis to justify their conclusions. Upon closer inspection, the actual conclusions of the review are that urgent attention needs to go into 'a properly... conducted randomized controlled trial with mortality as the end point' and in the meantime 'a review of the licensed indications for albumin use'.[17] A more detailed discussion can be found elsewhere.[18]

Some of the responses to the review, published electronically, contained new data. Jones and colleagues suggested that capillary leakage may explain the increased mortality, and presented data showing that albumin leakage was greater in critically ill patients than in patients after major surgery, in whom it was in turn greater than patients with polycythaemia.[104] Thus, infusion of albumin in the critically ill would not increase the intravascular albumin concentration, and would exacerbate interstitial oedema. Our preliminary data showing the toxicity of tacrolimus (FK506) in patients with a low concentration of albumin after liver transplantation represents a group that may benefit from maintaining a predetermined circulating concentration of albumin.[102] Data from the Netherlands Cancer Institute have shown that patients with peritoneal cancer undergoing prolonged surgery might also benefit from albumin therapy.[44]

Further electronic correspondence proposed explanations of why albumin might not work. It may be that the beneficial effects of albumin in the circulation, such as the binding of toxins, heavy metals and drugs, are detrimental outside of the circulation, given the increase in capillary permeability during critical illness.[61] There may also be adverse immunological effects of albumin transfusion that could explain the increase in mortality suggested by the meta-analysis.[5] More recently, the effects of albumin from different manufacturers and indeed different batches on adhesion molecules have been described.[68]

Conclusions

Albumin has well-established and important functions in health. Its kinetic and dynamic properties are significantly altered in the critically ill. There is no significant correlation between serum albumin concentration and COP in these patients. Drug binding by albumin is important in critically ill patients, but the increased free fraction of drugs in patients with hypoalbuminaemia does not necessitate treating the decreased serum albumin concentration.

The choice of fluid for resuscitation in the critically ill remains contentious. Despite the fact that a low serum albumin concentration is an independent predictor of morbidity, there is no evidence to support the use of albumin to treat hypoalbuminaemia or hypovolaemia in critically ill patients.[4 28 81 96 97] Future research needs to address why the theoretical advantages of albumin are not borne out in clinical practice. This may identify patients in whom albumin is the volume expander of choice. In the wake of the highlighted meta-analysis, there is an urgent need for properly constructed trials in the critically ill.

Declaration of conflicts of interest

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SHORT COMMUNICATIONS

Pulmonary artery catheterization and mortality in critically ill patients†

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Pulmonary artery catheters are widely used in intensive care, but evidence to support their widespread use is sparse. Some published data suggest that greater mortality is associated with use of these catheters. The largest study to date looked at >5500 patients in several centres in America and found a greater 30 day mortality in those patients receiving a pulmonary artery catheter. We tested the hypothesis that, on our intensive care unit, mortality was greater for those patients receiving a pulmonary artery catheter. Using a propensity score to account for severity of illness, the odds ratio for mortality in those patients receiving a pulmonary artery catheter was 1.08 (95% confidence interval 0.87–1.33). We believe that continued use of the pulmonary artery catheter is safe; a large randomized controlled trial examining outcome is unlikely to provide an adequate answer.

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Since its introduction in 1970, the pulmonary artery catheter[1] has become commonplace in intensive care practice. Pulmonary artery catheterization was first described in 1945[2] and from then until the 1970s was used in the catheter laboratory as a diagnostic tool. When it became possible to perform the procedure at the bedside in critically ill patients in the intensive care unit, the balloon-tipped pulmonary artery catheter became widely used as a guide to treatment. In 1996, over two million catheters were sold worldwide.[3]

The effectiveness of new techniques and treatments should ideally be evaluated before they are introduced,[4] but this is not always done. The pulmonary artery catheter was not evaluated in this way before being introduced. Despite this, many physicians believe it can guide treatment and provide useful physiological data. Several well conducted studies have shown an improvement in outcome when acting on data provided by the pulmonary artery catheter.[5–7] However, greater mortality has been demonstrated in some patients, most notably in those who have had a myocardial infarction.[8 9] It has proved difficult to conduct a randomized, controlled trial of pulmonary artery catheter use.[10]

In September 1996, Connors and colleagues published a paper examining the use of the pulmonary catheter in 5735 intensive care patients.[11] This multicentre study found greater mortality in patients receiving a pulmonary artery catheter. The paper was based on data collected as part of the SUPPORT[12] study, which was designed to look at decision-making and outcomes in patients with an estimated 6 month mortality of 50%. The study took place between 1989 and 1994 in five American teaching hospitals with patients in one or more of nine disease categories: acute respiratory failure, chronic obstructive pulmonary disease, congestive heart failure, cirrhosis, non-traumatic coma, colon cancer metastatic to the liver, non-small-cell cancer of the lung (stage III or IV) and multiple organ system failure with malignancy or sepsis. Not all patients with these conditions would commonly be given pulmonary catheters in European practice. The statistical techniques used by Connors and colleagues included the propensity score[13] to allow comparison between patients receiving or not receiving a pulmonary artery catheter while compensating for severity of illness and treatment selection bias

We examined the effect of the pulmonary artery catheter on intensive care mortality in all adult patients admitted over 7 yr to an intensive care unit in a large British teaching hospital. A propensity score was used to compensate for severity of illness between groups.

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Materials and methods

Data have been collected prospectively on all patients admitted to the intensive care unit at St James's University Hospital, Leeds, since 1984. The unit is based in a major teaching hospital and accepts patients from all specialties except neurosurgery and cardiothoracic surgery. The unit provides a regional tertiary referral service for patients with respiratory and renal failure, and a supraregional liver failure and transplant programme.

We examined patient characteristics, physiological, treatment and outcome data for 4182 patients aged >16 yr admitted between January 1990 and December 1996. Patient characteristics available included age, gender, race (Caucasian or non-Caucasian), length of intensive care stay, the need for readmission, APACHE II (Acute Physiology and Chronic Health Evaluation) score,[14] presence of acute renal failure, elective/emergency admission and physician's prediction of death. Treatment variables included insertion of a central venous catheter, insertion of an arterial cannula, treatment with epinephrine, norepinephrine, dopamine or dobutamine (separate variables) and the need for ventilation of the lungs. Outcome data were discharge from the intensive care unit or death on the intensive care unit. APACHE II data were based on the first 24 h of intensive care admission. The physician's prediction of death was a dichotomous variable, with patients being predicted to survive or predicted to die.

Following a univariate analysis, 15 variables were entered in a backward stepwise logistic regression analysis. Statistically significant variables, identified from the regression analysis, were used to calculate the propensity score. Variables in the final equation were acute renal failure, need for treatment with epinephrine, norepinephrine, dopamine and dobutamine, monitoring of arterial pressure and central venous pressure, physician's prediction of death and patient age. Variables excluded from the equation included gender, race, APACHE II score, duration of intensive care stay, need for elective (as opposed to emergency) admission and the need for subsequent readmission to the intensive care unit. The significant variables were entered into a logistic regression analysis with pulmonary artery catheter insertion during intensive care stay as the dependent variable. This gave the probability (from 0 to 1) of pulmonary artery catheter insertion occurring during a patient's intensive care stay, the 'propensity score'. Statistical analysis was performed using SPSS for Windows version 6, the receiver operator characteristic (ROC) plot was produced by Astute (University of Leeds) on Microsoft Excel 4, all running on Microsoft Windows 98 on a Dan 120 MHz Pentium computer.

The accuracy with which a propensity score predicts a treatment option can be tested using the ROC plot. The area under the ROC curve corresponds to the probability of the propensity correctly predicting if a patient receives a treatment or not (in this case a pulmonary artery catheter).

Table 1 Characteristics of 4182 intensive care patients

Variable	PA catheter (n=1849)	No PA catheter (n=2333)
Age**		
<50 yr	682 (37)	720 (31)
50–<60 yr	330 (19)	388 (17)
60–<70 yr	404 (22)	565 (24)
70–<80 yr	354 (19)	497 (21)
≥80 yr	79 (4)	163 (7)
Gender		
Male	1093 (59)	1364 (58)
Female	756 (41)	969 (42)
Race		
Caucasian	1798 (97)	2274 (97)
Non-Caucasian	51(3)	59 (3)
Elective*	192 (10)	395 (17)
Emergency*	1657 (90)	1938 (83)
Readmission	208 (11)	253 (11)
LOS**	3 (1, 8)	1 (1, 2)
APACHE II**	24 (24, 31)	15 (10, 22)
CVP*	1849 (100)	1928 (83)
Acute renal failure*	647 (35)	174 (7)
Arterial line*	1849 (100)	1953 (84)
Epinephrine*	829 (45)	149 (6)
Norepinephrine*	614 (33)	43 (2)
Dopamine*	1578 (85)	1010 (43)
Dobutamine*	555 (30)	163 (7)
Intubated*	1721 (93)	1654 (71)
Predicted to die*	756 (41)	309 (13)
Died*	794 (43)	293 (13)

Data presented as number (%) or median (25th and 75th percentiles) *$P<0.0001$ (chi-squared test) **$P<0.0001$ (Mann–Whitney U-test).

Bias in the propensity score can be investigated by examining subclasses of data based on the propensity score. If the score is valid it compensates for the covariates; within each class there should be only random differences in the distribution of covariates, which cancel each other out. This means that within each stratum, no factor retains a relationship with the exposure.[15] It is sufficient to look at only five equal groups, known as quintiles.[16] Quintiles based on the propensity score were examined to determine the distribution of the predictive variables for pulmonary artery catheter insertion.

The predictive value of the propensity in predicting the insertion of the pulmonary artery catheter was tested using a ROC curve.[16] The calculated propensity score and pulmonary artery catheterization were then investigated as the two potential predictors of mortality in intensive care, in a logistic regression model.

Subgroup analysis of the effect of the pulmonary artery catheter on mortality was performed based on (i) patients' APACHE II score on admission and on (ii) elective compared with emergency admission.

Results

There were 2456 male patients and 1726 females; their median age was 56.3 yr (interquartile range 42.8–70.5 yr), median APACHE II score 19 (interquartile range 12–27) and median length of stay 2 days (interquartile range 1–4 days). Further details of the patients are given in Table 1.

Patients who had a pulmonary artery catheter inserted were more likely to be younger, have renal failure, be treated with inotropes, have acute renal failure and have a prolonged stay in intensive care stay. Patients without a pulmonary artery catheter were more likely to be older, admitted electively and have a lower APACHE II score. There was no difference in the two groups with respect to gender, racial origin or previous intensive care unit admission.

There was an overall mortality of 1087/4181 (26%), comprising a mortality of 293/2333 (12.6%) in those without a pulmonary artery catheter and 794/1849 (42.9%) in those with a pulmonary artery catheter (chi-squared $P<0.0001$). The pulmonary artery catheter was, therefore, strongly associated with mortality when no adjustment had been made for severity of illness.

The propensity score had an area under the ROC curve of 0.88, indicating good predictive value for insertion of the pulmonary artery catheter (Connors and colleagues obtained a propensity score of 0.83).

The median propensity score was 0.797 (interquartile range 0.456–0.947) for patients who had a pulmonary artery catheter inserted and 0.176 (interquartile range 0.086–0.337) for those who did not have a pulmonary artery catheter inserted.

The calculated propensity score and pulmonary artery catheterization were then investigated as the two potential predictors of mortality, in intensive care, in a logistic regression model. The cut-off value for the propensity score was 0.5. The propensity score was predictive of death, (odds ratio (OR) 45; 95% confidence interval (CI) 34.7–58.3). Use of the pulmonary artery catheter was not predictive of death (OR 1.08; 95% CI 0.87–1.33).

Analysis of patients according to APACHE II score did not demonstrate a deleterious effect of pulmonary artery catheter use in any group.

In patients with an APACHE II score of <20, the presence of a pulmonary artery catheter was not predictive of death (OR 1.14; 95% CI 0.7–2.5), but the propensity score was (OR 75.8; 95% CI 34.8–164.7). In patients with an APACHE II score of 20–25, pulmonary artery catheter insertion was not predictive of death (OR 1.3; 95% CI 0.8–2.15) but the propensity score was (OR 11.27; 95% CI 5.3–24). In patients with an APACHE II score of >25, the pulmonary artery catheter was not predictive of death (OR 0.89; 95% CI 0.64–1.25) but again propensity score was predictive (OR 7.43; 95% CI 4.48–12.3).

In patients admitted electively to the intensive care unit, the pulmonary artery catheter was not predictive of death (OR 1.9; 95% CI 0.57–6.14), but propensity score was predictive (OR 330; 95% CI 54.2–2006).

Quintile analysis showed that the predictor variables were evenly distributed between interventional groups, with the exception of central venous and arterial cannulae in the lowest quintile. This is unlikely to be important in the absence of a treatment effect from the pulmonary artery catheter.

Discussion

The data we have examined show no increase in mortality in those patients receiving a pulmonary artery catheter, nor do we demonstrate a beneficial effect of its use. These results were observed after correction for treatment bias using a propensity score. In observational studies, patients are not assigned to treatment groups randomly. It is, therefore, inevitable that some patient variables are over-represented in one group. Consequently, it is difficult to interpret direct comparison between the two groups.

Previous observational studies found an increase in mortality in patients receiving a pulmonary artery catheter. It has been claimed that patients who were sicker and more likely to die received the pulmonary artery catheter and this underlying severity of disease led to the increase in mortality, rather than the pulmonary artery catheter itself.[9] The ideal is a randomized controlled trial, where all variables are represented equally in each treatment group. Where such a trial is not possible, a technique used to overcome this problem is the propensity score, which describes the probability of assignment to a given treatment given a vector of observed covariates. Propensity score is calculated using logistic regression analysis of the variables that lead to a given treatment. It is dependent on identifying variables leading to exposure and is liable to bias owing to failure to include important variables that lead to exposure. In effect, the propensity score represents the probability that a patient will receive a given treatment, taking into account the individual patient's variables that are believed to lead to that treatment. The propensity score can then be used with the treatment it predicts in order to investigate the effect of the treatment, independently of the variables leading to that treatment.

The pulmonary artery catheter is a monitoring device; it is generally used to obtain haemodynamic data on patients which may be used to guide treatment. Any possible effect on mortality could result from a direct effect or from the way in which the information obtained from the catheter is used to guide treatment.

Direct effects can be divided into the immediate problems of central line insertion (damage to vessels,[17] infection,[18] cardiac arrhythmias, etc.) and the later risk of infective endocarditis. It is unlikely that these complications are responsible for the increased mortality previously reported with pulmonary artery catheters. The reported increase in mortality with the use of pulmonary artery catheters is probably, therefore, an indirect effect of their use or caused by problems with studying their use.

The therapy received by a patient plays a major role in determining the outcome. In therapies based on data obtained from the pulmonary artery catheter, the catheter may act as an indicator of excess mortality of that therapy. It is easier to blame the catheter than the treatment for which it is being used. The use of supranormal oxygen delivery was once an aim of treatment guided by data obtained from the pulmonary artery catheter. A recent study has demonstrated that this therapeutic regimen may be harmful to patients.[19] As the Connors study was multicentre and observational, it is possible that, in some patients in that study, the pulmonary artery catheter was used to obtain supranormal oxygen delivery.

The use of variables in our propensity score indicating the use of inotropes allows compensation to be made in the final analysis reflecting therapeutic intervention. This use of inotropes was recorded at any point during a patient's illness on the intensive care unit, and so reflected the change in a patient's condition over time and their response to treatment. The variables used in the construction of the propensity score in the Connors paper did not reflect therapeutic intervention but predominantly reflected the patient's physiological status on admission to the intensive care unit.

Interpretation of the data obtained from the pulmonary artery catheter has been shown to be poor in studies in America[20] and Europe.[21] There are differences between intensive care practice in France and America,[22] and probably also between the UK and USA. It is likely that some patients in the American study would not have been admitted to intensive care in the UK. The SUPPORT study showed differences in medical practice between the five hospitals studied and between different physicians. The results we present are obtained from one intensive care unit, where practice is consultant led and protocol driven. We use pulmonary artery catheters extensively.[23]

We studied all adult patients admitted to an intensive care unit, classed all patients who had a pulmonary artery catheter inserted at any time in the pulmonary artery group and examined patients' need for cardiovascular and renal support throughout their stay. This provides an overall examination of the effects of the pulmonary artery catheter. Connors and colleagues produced a subgroup analysis based on diagnosis but we did not attempt this because we could not match our groups with those of Connors and colleagues. Smaller groups would have a different propensity score for pulmonary artery catheter insertion (leading to lack of power in the analysis). Modelling treatment effects would also be more difficult in small groups of patients.

While we have not demonstrated an increase in mortality attributable to the use of pulmonary artery catheters, we have failed to demonstrate a beneficial effect. This may be because there is no beneficial effect. It could also be because the benefit accruing from additional clinical information has little effect on individual patients, but rather informs practice as a whole. Would the results in patients who did not have pulmonary artery catheters have been as good without the accumulated experience resulting from years of using pulmonary artery catheters and familiarity with the likely haemodynamics in a given clinical situation? If we were to abandon the pulmonary artery catheter, would this skill base decay and, if so, over how long? It is unlikely that a simple head-to-head trial could answer such questions. A randomized, controlled trial of pulmonary artery catheters is required to assess their benefit, but our results suggest that such a study, even with very large numbers of patients, would have insufficient power to demonstrate an effect on mortality. Organizational differences between intensive care units, together with the change in practice that might occur as a result of participation in such a trial, would need to be taken into account in the analysis of such a study.

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Fentanyl versus sufentanil: plasma concentrations during continuous epidural postoperative infusion in children

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No pharmacokinetic data are available with respect to the plasma concentrations and fentanyl or sufentanil during epidural administration in children. This double-blind randomized study included 12 children (5–12 yr). Patients in group F were given an epidural loading dose of fentanyl 1.5 $\mu g\ kg^{-1}$ and in group S sufentanil 0.6 $\mu g\ kg^{-1}$. Both groups then received a continuous epidural infusion of bupivacaine 5 mg kg^{-1} day^{-1} with either fentanyl 5 $\mu g\ kg^{-1}\ day^{-1}$ or sufentanil 2 $\mu g\ kg^{-1}\ day^{-1}$. An epidural PCA system was also given to the children (bolus: bupivacaine 0.2 mg kg^{-1} and fentanyl 0.2 $\mu g\ kg^{-1}$ or sufentanil 0.08 $\mu g\ kg^{-1}$). Maximal median concentrations of plasma (0.117–0.247 ng ml^{-1} for fentanyl and 0.027–0.074 ng ml^{-1} for sufentanil) were reached approximately 30 and 20 min respectively after the loading doses. These values were similar to those measured after 48 h.

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Keywords: analgesia, postoperative; analgesics opioid, fentanyl; analgesics opioid, sufentanil; analgesic techniques, epidural; children

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Epidural bupivacaine has been shown to provide effective postoperative analgesia in paediatric patients. Bupivacaine toxicity may cause convulsions and cardiovascular depression. Therefore, it has been recommended that an opioid should be combined with bupivacaine rather than increasing the infusion rate of bupivacaine. The efficacy of a combination of fentanyl with bupivacaine has been reported.[1] However, only two studies report the epidural administration of sufentanil in children for postoperative analgesia.[2 3] Furthermore, no paediatric data are available about plasma concentrations after continuous and prolonged epidural administration of fentanyl or sufentanil. Therefore, we investigated this in children receiving epidural fentanyl or sufentanil at doses giving similar analgesia.

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Table 1 Plasma concentrations (ng ml^{-1}) of fentanyl (children 1–6) and sufentanil (children 7–12) during epidural administration. ND=not determined

Fentanyl group	**Child 1**	**Child 2**	**Child 3**	**Child 4**	**Child 5**	**Child 6**
Age (yr)	11	8	9	9	8	6
Surgery	Foot	Pelvis	Pelvis	Foot	Foot	Tibia
No. PCEA boluses	6	27	13	8	9	1
Time						
5 min	0.058	0.118	0.064	0.213	< 0.05	0.073
10 min	0.085	0.172	0.155	0.363	0.067	0.118
20 min	0.16	0.221	0.184	0.43	0.117	0.188
30 min	0.181	0.222	0.217	0.381	0.12	0.247
60 min	0.155	0.249	0.133	0.347	0.099	0.236
120 min	0.058	0.208	0.141	0.25	0.085	0.177
6 h	0.074	0.191	0.104	0.16	0.184	0.216
24 h	0.098	0.245	0.106	0.24	0.14	ND
48 h	0.142	0.261	0.221	0.172	0.229	ND
Sufentanil group	**Child 7**	**Child 8**	**Child 9**	**Child 10**	**Child 11**	**Child 12**
Age (yr)	7	6	11	11	5	8
Surgery	Pelvis	Pelvis	Foot	Foot	Foot	Tibia
No. PCEA boluses	10	8	3	1	10	5
Time						
5 min	0.022	<0.02	0.026	<0.02	0.061	0.047
10 min	< 0.02	<0.02	0.046	0.022	0.069	0.059
20 min	0.041	<0.02	0.022	0.027	0.07	0.074
30 min	0.042	<0.02	0.048	0.025	0.05	0.07
60 min	0.032	<0.02	0.045	0.018	0.028	0.058
120 min	<0.02	<0.02	0.037	0.026	<0.02	0.04
6 h	<0.02	<0.02	0.036	0.025	<0.02	0.03
24 h	<0.02	0.049	0.049	0.039	<0.02	0.038
48 h	0.024	ND	0.058	0.06	0.051	ND

Methods and results

After approval of the study by the Ethical Human Studies Committee of our University Hospital and written parental consent had been obtained, 12 children (5–12 yr) scheduled for postoperative epidural analgesia after orthopaedic surgery were enrolled in this prospective, randomized, double-blind clinical trial. Twenty minutes after premedication with midazolam 0.3 mg kg^{-1}, anaesthesia was induced by inhalation of halothane or sevoflurane. Endotracheal intubation was facilitated with atracurium 5 mg kg^{-1} and anaesthesia was maintained with an expired fraction of 0.8% isoflurane in nitrous oxide/oxygen (FI_{O_2}=0.5). Ventilation was controlled in order to maintain normocapnia. Children were placed in the lateral position for insertion of a lumbar epidural catheter before surgery. The epidural test dose consisted of 0.5% bupivacaine 0.1 ml kg^{-1} with epinephrine (1/200 000). Before surgery, all children received a bolus dose of 0.75 ml kg^{-1} of a 50/50% mixture of 0.5% bupivacaine and 1% lidocaine, with epinephrine. The patients were allocated randomly to receive either fentanyl (group F) or sufentanil (group S). Patients were given an epidural dose of fentanyl 1.5 μg kg^{-1} in group F and of sufentanil 0.6 μg kg^{-1} in group S. Immediately after the epidural loading dose had been given, a continuous epidural infusion was started with bupivacaine 5 mg kg^{-1} day^{-1} plus fentanyl 5 μg kg^{-1} day^{-1} in group F and sufentanil 2 μg kg^{-1} day^{-1} in group S. In the recovery room, after tracheal extubation and once the children were completely awake, an epidural patient-controlled analgesia (PCEA) system was given to the children. They could self-administer boluses of bupivacaine 0.2 mg kg^{-1} with fentanyl 0.2 μg kg^{-1} or sufentanil 0.08 μg kg^{-1} in groups F and S respectively. Lock-out time was 1 h, with a maximal number of two boluses per 4 h. The maximal daily total doses of epidural bupivacaine, fentanyl and sufentanil were 7.4 mg kg^{-1}, 7.4 μg kg^{-1} and 2.96 μg kg^{-1} respectively. The continuous and PCEA epidural administration was planned for the 48 h after operation. Randomization was performed by the pharmacist of the hospital, who prepared the vial of opioids for the double-blind procedure.

Measurements of plasma fentanyl and sufentanil plasma were performed on venous samples withdrawn 5, 10, 20, 30 and 60 min and 2, 6, 24 and 48 h after the loading dose in six patients from each group, using a radioimmunological method. The limit of quantification was 0.020 ng ml^{-1} for sufentanil and 0.05 ng ml^{-1} for fentanyl. Pain was evaluated every 3 h with a standard visual analogue pain scale graded from 0 to 100, except when the child was asleep. The first evaluation was performed by the child on arrival in the surgical ward. The number of PCEA-satisfied demands for the 48 h after operation was recorded.

Patient characteristics are presented in Table 1. Epidural analgesia was interrupted prematurely in children 6 and 8 at the 15 and 20th hour respectively because of accidental removal of the epidural catheter. In one other child (number 12), the study was stopped at the 30th hour because of a surgical complication. Among the 52 plasma determinations performed in group F and the 51 performed in group S, 1 and 14 respectively were below the limit of quantification ($P<0.001$). The maximum concentrations (0.117–0.247 ng ml^{-1} for fentanyl and 0.027 and 0.074 ng ml^{-1} for sufentanil) had been reached by approximately 30 min after the loading dose for fentanyl and by 20 min for sufentanil. Analgesia was excellent in both groups. The median (25–75%) number of self-administered boluses was similar in the two groups: 8.5 (5–11) in group F and 6.5 (4–7.25) in group S.

Comments

The initial systemic absorption of sufentanil is very rapid. The relative delay of the peak plasma concentration of sufentanil observed in our patients was similar to that reported previously in adults.[4] The plasma concentrations of fentanyl or sufentanil reached with our epidural regimens were very low, with little suggestion of accumulation at 24 and 48 h. The excellent quality of analgesia associated with very low plasma concentrations of sufentanil suggest a spinal action of sufentanil. Other investigators have reported plasma concentrations of sufentanil or fentanyl below the minimal effective concentration necessary for systemic analgesia after epidural injection.[5] With intravenous infusion, a serum sufentanil concentration above 0.03 ng ml^{-1} seems to be necessary for analgesia.[6 7] However, it has been suggested that the epidural and i.v. doses of sufentanil required for analgesia are similar.[8]

The plasma concentrations of sufentanil and fentanyl that are not associated with risk of respiratory depression are not well established. The target concentration of fentanyl for analgesia is considered to be above 1.5 ng ml^{-1} and thus induces significant alteration in the carbon dioxide response.[9] A 38% decrease in the carbon dioxide response slope has been reported in association with a mean plasma concentration of 0.95 (SD 0.2) ng ml^{-1}.[10] Respiratory depression has been described in one adult despite a plasma concentration below 1 ng ml^{-1}, whereas infants and children in the same study had respiratory depression only when the fentanyl concentration exceeded 1 ng ml^{-1}.[11] For sufentanil, a plasma concentration >0.25 ng ml^{-1} is considered to be efficacious with self-spontaneous ventilation when administered i.v.

In the first report of epidural administration of sufentanil in children, the slope of the carbon dioxide ventilatory response curve decreased significantly from 1.1 before sufentanil to 0.68 litre min^{-1} mm Hg^{-1} 30 min after epidural administration.[2] A higher dose (0.75 μg kg^{-1}) than that used in our study was administered, and the plasma concentrations were low (0.1 ng ml^{-1}).

The low concentrations of sufentanil and fentanyl measured in our study do not eliminate completely the possibility of respiratory depression, and monitoring the sedation score and respiratory rate remains absolutely necessary. Nevertheless, fentanyl and sufentanil are highly lipid-soluble opioids and migrate less than morphine in the cerebral spinal fluid. They are less likely to cause delayed respiratory depression after epidural administration.

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Peribulbar anaesthesia with 1% ropivacaine and hyaluronidase 300 IU ml^{-1}: comparison with 0.5%bupivacaine/2% lidocaine and hyaluronidase 50 IU ml^{-1}

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The low toxicity of ropivacaine makes it attractive for peribulbar anaesthesia. However, its motor-sparing properties are undesirable when akinesia is important. Hyaluronidase (300 IU ml^{-1}) promotes the onset and quality of peribulbar blockade when used with other agents. We investigated the onset and quality of ocular akinesia in 80 patients randomized to receive 1% ropivacaine plus hyaluronidase 300 IU ml^{-1} (group 1), or bupivacaine 0.5%/ Lidocaine 2% plus 50 IU ml^{-1} hyaluronidase (group 2). Ocular akinesia was scored from 0 (no movement) to 8 (full movement) every 2 min for 20 min. The groups showed no difference in the rate of onset or degree of akinesia achieved (analysis of variance with repeated measures; P=0.34). Sixty per cent of patients in group 1 and 55% in group 2 achieved akinesia scores of ≤4 by 6 min (χ^2 test; P=0.5). We conclude that both peribulbar solutions produce equivalent onset and quality of ocular akinesia.

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Ropivacaine has the potential advantage of reduced cardiovascular and neurological toxicity compared with other local anaesthetics that are commonly used for peribulbar anaesthesia. However, the motor sparing attributed to ropivacaine[1] is a potential disadvantage that might reduce the onset or extent of motor block required for ophthalmic surgery. Previously it was found that combining a high concentration of hyaluronidase (300 IU ml^{-1}) with a bupivacaine/lidocaine mixture improved the onset and quality of peribulbar block.[2] However, there are few data on the addition of high concentrations of hyaluronidase to ropivacaine. Therefore, we compared a mixture of 1% ropivacaine with hyaluronidase 300 IU ml^{-1} with our standard 1:1 mixture of 0.5% bupivacaine/2% lidocaine with hyaluronidase 50 IU ml^{-1}. The onset and quality of block were compared.

Methods and results

After having obtained Research Ethics Committee approval, we recruited 80 consecutive ASA I–III Chinese outpatients undergoing phacoemulsification cataract surgery in a randomized double-blind study. Patients refusing consent, taking anticoagulants, allergic to amide local anaesthetics or hyaluronidase, or with a single eye, were excluded. After they had given written informed consent, the patients were randomized to receive peribulbar anaesthesia using either 1% ropivacaine with hyaluronidase 300 IU ml^{-1} (group 1) or a 1:1 mixture of 0.5% bupivacaine/2% lidocaine with adrenaline 1:200 000 and hyaluronidase 50 IU ml^{-1} (group 2).

Intravenous access and standard monitoring were established, and one drop of 1% tetracaine was administered topically. Anaesthetic solutions were prepared individually immediately before injection. The investigators performing the injections (M.W.I.T.) and assessments (D.K.W.) were blinded to the solutions used. A two-injection technique was used, consisting of inferolateral and superior injections using a 22 mm, 25 gauge needle. Local anaesthetic was injected until peribulbar fullness was observed or to a maximum of 8 ml. Ocular pressure of 30 mm Hg was applied for 20 min, and was removed at 2 min intervals to assess residual ocular movement. Movement in the superior, inferior, medial and lateral directions was scored as 0 (no

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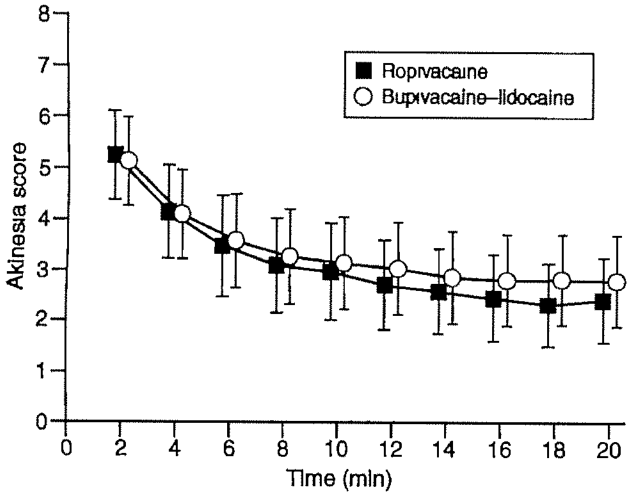

Fig 1 Onset of akinesia in patients receiving ropivacaine (group 1) and bupivacaine plus lidocaine (group 2).

movement), 1 (up to 2 mm movement) or 2 (>2 mm movement); this gave a range from 0 (complete akinesia) to 8 for each assessment.[3]

Surgery started after 20 min. Patients were asked to grade discomfort during injection and during surgery on a 5-point ordinal scale (none, mild, moderate, severe, worst ever). The surgeon graded operating conditions on a 10 cm visual analogue scale (VAS; 0=impossible, 10=ideal).

The principal end-point was the rate of onset and the quality of ocular akinesia. Previously, successful block was defined as an ocular mobility score $\leqslant 4$.[3] Prospective power analysis showed that a sample size of 40 patients per group would have 80% power at the 0.05 level of significance to detect a 30% difference in the proportion of patients with an ocular mobility score $\leqslant 4$ at 6 min, assuming an expected proportion of approximately 84% in the control group.[3] Data were analysed using analysis of variance for repeated measures, Student's t test, the χ^2 test and the Mann–Whitney U test as appropriate. Values of $P<0.05$ were considered statistically significant.

Patient characteristics were similar between groups. Both groups had approximately twice as many women as men, with a mean age of 76 (SD 9) yr in group 1 and 74 (8) yr in group 2. The mean volume of anaesthetic injected was similar (6.7 (0.7) ml in group 1 and 6.7 (0.8) ml in group 2).

There were no differences between groups in the rate of onset of block or the degree of akinesia achieved (P=0.34; Fig. 1). Sixty per cent of patients in group 1 and 55% in group 2 achieved akinesia scores of $\leqslant 4$ at 6 min (P=0.5). Because of discomfort during surgery, one patient in group 1 required additional topical anaesthesia, while two patients required topical anaesthesia and two required subtenon's injection in group 2. These differences were not statistically significant. Operating condition scores were similar (group 1, 7.6 (2.2) cm; group 2, 7.1 (2.9) cm; P=0.6).

Eighty-five per cent of patients in group 1 and 87.5% in group 2 reported no or mild discomfort during injection (P=0.8), and only 5% in each group reported severe discomfort. During surgery, there was no complaint of discomfort in 75% of patients in each group. The remainder complained of mild discomfort, and one patient in group 1 reported moderate discomfort.

Comment

We found that 1% ropivacaine with 300 IU ml^{-1} hyaluronidase gave onset and quality of peribulbar block equivalent to 0.5%bupivacaine/2%lidocaine with 50 IU ml^{-1} hyaluronidase.

Before commencing our study, the only published data on peribulbar ropivaçaine were comparisons of ropivacaine/lidocaine with bupivacaine/lidocaine mixtures.[3] We wished to determine whether ropivacaine as the sole anaesthetic could provide satisfactory akinesia for ocular surgery, particularly as other clinical applications have demonstrated motor sparing properties.[1] However, before commencing the study, our impression with 1% ropivacaine was that onset of akinesia was delayed. Previous findings demonstrate that a high concentration of hyaluronidase (300 IU ml^{-1}) in peribulbar local anaesthesia promotes the speed of onset and quality of block,[2] hence we opted for a combination of 1% ropivacaine and high-dose hyaluronidase. This was compared with our standard peribulbar local anaesthetic mixture as the control.

After we had commenced our study, a number of other studies of peribulbar ropivacaine combined with hyaluronidase 0–75 IU ml^{-1} were published, and they found this to be as effective as 0.75% bupivacaine or 0.5% bupivacaine/2% lidocaine mixtures.[4 5 6] Differences in methods between studies make direct comparison difficult. These include site(s) of injection, akinesia scoring methods, the definition of successful block, indications for and methods of supplementation, and the type of surgery. We used a two-injection technique according to our routine practice. Our method of assessing ocular mobility was simple and semiquantitative. We felt this was more objective and reproducible than qualitative methods. Our surgeons tolerated considerable eye movement. This was largely because we studied patients undergoing phacoemulsification, which is increasingly being performed under topical anaesthesia alone. An 'unsuccessful block' therefore related in practice to problems with analgesia rather than akinesia, with a correspondingly low supplementation rate compared with some other studies.[4]

Only one other study has been published using 300 IU ml^{-1} peribulbar hyaluronidase.[2] No adverse effects specifically related to hyaluronidase were reported. Although we found that adding this dose of hyaluronidase to 1% ropivacaine resulted in an effective mixture for peribulbar block, the successful use of ropivacaine alone, or with lower concentrations of hyaluronidase, has now been reported.[4 5 6] Huha *et al.* [6] found that plasma concentra-tions of ropivacaine approached the reported greatest tolerated concentration in four of 11 patients using 1% ropivacaine and hyaluronidase 7.5 IU ml^{-1}. The pharmacokinetic effects of higher hyaluronidase concentrations are unknown.

In conclusion, we have found that 1% ropivacaine with hyaluronidase 300 IU ml^{-1} is a suitable mixture for peribulbar block, with onset and quality of anaesthesia similar to those achieved with bupivacaine/lidocaine. Further work is required to determine the effect of high concentrations of hyaluronidase on plasma concentrations of ropivacaine and the duration of block.

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Lack of pre-emptive analgesic effects of local anaesthetics on neuropathic pain

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We investigated the significance of pre-emptive analgesia using a well-known model of neuropathic pain in rats. Lignocaine, bupivacaine or saline was applied locally to the left L5–L6 spinal nerve before or 4 days after nerve injury. Mechanical allodynia was then evaluated before and after injury. Pre- and post-injury treatment with local anaesthetics both resulted in a two- to threefold increase in the pain threshold, as manifested by a significant increase in von Frey measurements. However, this effect lasted only 24 h. Our study in rats questions the beneficial effect of a single dose of local anaesthetic as pre-emptive analgesia.

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Keywords: anaesthetics local, bupivacaine; anaesthetics local, lignocaine; pain, neuropathic; rats

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Pre-emptive analgesia, the administration of analgesics before tissue damage, aims to reduce both postoperative pain and the subsequent development of chronic pain after surgery. Studies in animals have shown that tissue damage produces significant changes in neuronal processing, including central sensitization, alteration in

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neuronal phenotype and the loss of neurons in the dorsal root ganglion with associated synaptic plasticity.[1] Both basic science and recent clinical studies have shown that such changes may be attenuated to varying degrees if analgesic agents are administered before tissue injury.[2]

Local anaesthetics are useful in alleviating both acute and chronic pain through their inhibitory actions on sodium channels. The use of local anaesthetic agents in pre-emptive analgesia has been investigated in two inflammatory models of acute pain, the formalin test and the carrageenan test. However, very few investigations have used animal models of neuropathic pain.[3]

The purpose of our study was to test the efficacy of the direct application of two commonly used local anaesthetics, lignocaine and bupivacaine, onto the nerves before or after injury, using the Chung model of segmental spinal nerve injury.[4] In this model, rats develop neuropathic pain with behavioural evidence of hyperalgesia and allodynia within 24 h of nerve ligation, which peaks within 7 days and may persist for several weeks.[4]

Methods and results

The experiments were approved by the Animal Care and Use Committee of The University of Texas Medical Branch and performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Thirty male Sprague–Dawley rats (Harlan Sprague–Dawley, Harlan Industries, Indianapolis, IN), weighing 150–200 g, were used. One week after the animals had been acclimatized to the laboratory conditions, baseline (before surgery) quantitative von Frey measurements were recorded and the animals were randomly assigned to one of three experimental groups: group I, saline; group II, 2% lignocaine and group III, 0.5% bupivacaine. Animals in each of the three groups were treated with either of the local anaesthetics or saline before nerve injury. Then the animals were prepared for measurements of chronic neuropathic pain behaviour, as described by Kim and Chung.[4] Briefly, the rats were anaesthetized with halothane in oxygen (halothane concentration of 2 vol% for induction and 0.8 vol% for maintenance). Animals were placed in the prone position, skin infiltration was done with saline (group I), 2% lignocaine (group II) or 0.5% bupivacaine (group III), and midline skin incisions at L4–S2 were made, followed by separation of the paraspinal muscles from spinous processes. The transverse process of L6 was then carefully removed. Once the left L5 and L6 spinal nerves had been identified, they were bathed with saline (group I), 2% lignocaine (group II) or 0.5% bupivacaine (group III) for 10 min. The left L5–L6 spinal nerves were then ligated tightly with 6–0 silk thread, and the wound was closed. At the end of surgery, anaesthesia was discontinued and the animals were awakened and placed back into their cages with food pellets and water ad libitum under the same environmental conditions as previously. The mechanical allodynia threshold was measured using von Frey filaments, as described below, every day for 7 days. To avoid the effects of the circadian cycle, all studies were performed during the same period (9 a.m. to 12 p.m.) on each of the experimental days.

Fourteen additional Sprague–Dawley rats were used to study the effect of 0.5% bupivacaine or saline when applied 4 days after injury. These animals were surgically prepared for the study in the same manner as the animals discussed above, except that their ligated L5–L6 spinal nerves had to be exposed again under anaesthesia in order to infiltrate the nerves with saline (group IV) or 0.5% bupivacaine (group V) 4 days after ligation.

Behavioural tests

All animals were tested for quantitative changes in pain threshold, as measured by the use of von Frey filaments. Before the von Frey measurements were made, each rat was placed on a metal mesh floor and covered with a plastic box (8×8×18 cm) and allowed 30 min to acclimatize. Thereafter, light mechanical stimuli using sufficient force to cause light buckling of the filament was applied to the plantar surface of the left foot using different strengths of von Frey filaments (Stoelting, Woodale, IL, USA). In brief, von Frey filaments with incremental stiffness (0.3–15 g) were applied serially to the paw in ascending or descending order of stiffness depending on the foot withdrawal response of the rat. The maximum and minimum cut-offs were at 15 and 0.3 g respectively. A single trial of stimuli consisted of five applications of a von Frey filament every 4 s to the plantar surface of the left hind paw perpendicularly for about 3–4 s. Brisk foot withdrawals (at least three times out of five applications) in response to normally innocuous mechanical stimuli using von Frey filaments were considered positive; no response was considered negative. Depending on the positive or negative response, subsequent filaments were applied in order of descending and ascending intensity respectively.

The baseline threshold value of von Frey measurement was 12.6 (SEM 1.1), 12.8 (0.8), 13.7 (0.7), 15 (0) and 15 (0) g for groups I, II, III, IV and V respectively. All the animals developed significant mechanical allodynia 24 h after spinal nerve ligation (Fig. 1). Pretreatment with either lignocaine or bupivacaine (groups II and III respectively) increased the threshold of mechanical allodynia compared with the control group (group I). However, this effect lasted only 24 h. Similarly, when bupivacaine was used after injury, its effect in alleviating mechanical allodynia lasted only 24 h. Neither pretreatment nor post-treatment with saline altered the development of mechanical allodynia.

Comment

Tissue and nerve damage and the subsequent transmission of neural impulses from the surgical site to the spinal cord mark the beginning of a process of central neural

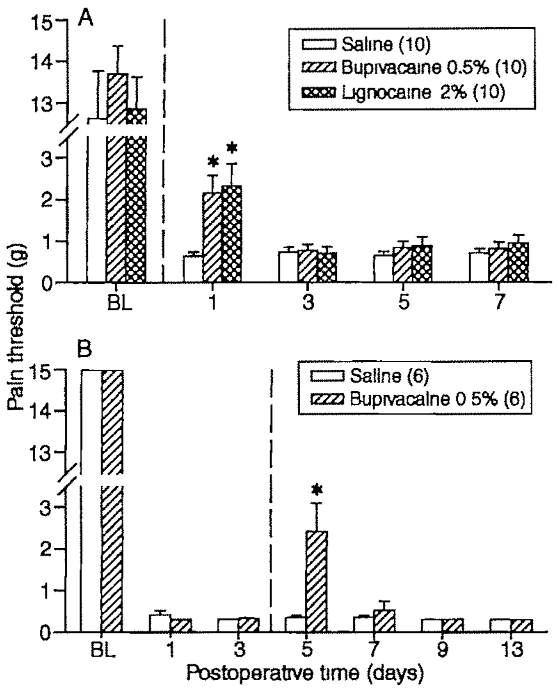

Fig 1 The effects of treatment with 2% lignocaine and 0.5% bupivacaine before injury (A) and 0 5% bupivacaine treatment after injury (B) on mechanical allodynia. Nerve injury was induced by tightly ligating the left L5–L6 spinal nerves in rats All the data are expressed as mean ± SEM. Statistical analysis was done by analysis of variance followed by Dunnett's *post hoc* test and Student's *t*-test where appropriate.*Significant difference ($P<0.05$) compared with the saline control group BL, Baseline, before surgery

sensitization that may be enhanced by other noxious perioperative events. The segmental spinal nerve injury model (Chung's model) is a well-established model used to induce neuropathic pain behaviour in rats. However, a meticulous surgical technique must be used in order to minimize the damage to the L4 spinal nerve, which can affect locomotor activity and the withdrawal response to various stimuli. Although no animal was excluded from this study because of dragging of the left hind limb (a sign of a damaged L4 spinal nerve), five rats were excluded from the study because of abnormal presurgical baseline von Frey measurements.

Although both pretreatment with 2% lignocaine or 0.5% bupivacaine and post-treatment with 0.5% bupivacaine slightly attenuated mechanical allodynia, all the animals remained significantly allodynic throughout the experimental period. This effect lasted only 24 h, which, although it is a short time, is considerably longer than expected from the half-life of the drugs. These results are consistent with the findings of Dougherty and colleagues,[3] who studied the differential influence of local anaesthetic upon two models of experimentally induced peripheral mononeuropathy in the rat, the partial constriction neuropathy (PCN) model and the partial transection neuropathy (PTN) model. They found that the PCN but not the PTN model showed an increase in pain threshold to the local application of anaesthetics at the time of injury. This was consistent with the previous observations made by Gonzales-Darder, whereby autotomy in rats was diminished in magnitude but unchanged in onset after application of anaesthetic to the sciatic nerve before transection.[5] Furthermore, Mao and colleagues[6] reported that a single perineural injection of bupivacaine (0.5%) on day 3 after nerve ligation reduced thermal hyperalgesia when assessed 24 h after injection, and that this effect lasted for under 48 h. This is consistent with our findings in the present study (Fig. 1B), even though we infiltrated the nerves with local anaesthetic 10 min before injuring (ligating) them in addition to 4 days afterwards. In clinical studies, Nikolajsen and colleagues[7] reported that perioperative epidural block that was started about 18 h before the amputation and continued into the postoperative period did not prevent phantom or stump pain.

Although the role of pre-emptive analgesia in neuropathic pain is still not clear, we speculate that it may not prevent the barrage of neural discharges necessary for the development of neuropathic pain at the time of injury. In the present study, although the use of the local anaesthetics before nerve injury seems to have delayed the transmission of pain impulses to the central nervous system, it did not prevent the occurrence of neuropathic pain.

Thus, the important question remains: when is the best time to administer local anaesthetics in order to derive the maximum benefit from their pre-emptive analgesic effects?

In conclusion, our present pilot study suggests that the application of a single dose of local anaesthetic onto an injured nerve may not be a clinically effective means of preventing neuropathic pain. Therefore, further blinded studies are necessary to ascertain the combination of dosage, time frame and route of administration of local anaesthetics that is most effective in preventing neuropathic pain.

Acknowledgement

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British Journal of Anaesthesia 85 (4) 623–5 (2000)

Comparison of intubating conditions following propofol and succinylcholine with propofol and remifentanil 2 $\mu g\ kg^{-1}$ or 4 $\mu g\ kg^{-1}$

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We evaluated the intubating conditions, haemodynamic responses and duration of apnoea in 60 healthy adult patients after propofol 2 mg kg^{-1} combined with either a bolus of remifentanil 2 $\mu g\ kg^{-1}$ or 4 $\mu g\ kg^{-1}$, or succinylcholine 1 mg kg^{-1}. Patients intubated following remifentanil showed dose-dependent intubating conditions, similar at 4 $\mu g\ kg^{-1}$ to the conditions produced with succinylcholine. Post-induction mean arterial pressure decreased from baseline values by 21% ($P<0.0001$), 28% ($P<0.0001$) and 8% ($P>0.05$) in the remifentanil 2 $\mu g\ kg^{-1}$, remifentanil 4 $\mu g\ kg^{-1}$ and succinylcholine 1 mg kg^{-1} groups, respectively. The mean (SD) duration of apnoea following induction was 9.3 (2.6) min and 12.8 (2.9) min in the remifentanil 2 $\mu g\ kg^{-1}$ and 4 $\mu g\ kg^{-1}$ groups, and 6.0 (0.9) min in the succinylcholine group ($P<0.001$ between groups).

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Keywords: analgesics opioid, remifentanil; anaesthetics i.v., propofol; neuromuscular block, succinylcholine; intubation tracheal

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Neuromuscular blocking drugs, particularly succinylcholine, may cause serious side effects but remain in clinical use to facilitate tracheal intubation due to a lack of suitable alternatives.[1] A combination of propofol and alfentanil has been demonstrated to reliably facilitate intubation without the use of neuromuscular blocking agents.[2 3] Remifentanil is a new potent fentanyl derivative with a unique metabolic profile and plasma clearance considerably faster than alfentanil.[4] These properties make remifentanil the opioid of choice to facilitate tracheal intubation, and subsequently allow a rapid return of spontaneous respiration and airway reflexes. In this study, we have compared the intubating conditions, haemodynamic changes and duration of apnoea in healthy adults following induction of anaesthesia with propofol in combination with either succinylcholine or varying doses of remifentanil.

Methods and results

With Ethics Committee approval and written informed consent, 60 ASA 1 and 2 non-obese, elective surgical patients, aged between 18 and 65 yr who required intubation for their proposed surgery were studied. Those on obstetric, neurosurgical or ophthalmic lists, those with Mallampati scores greater than 2 or with gastro-oesophageal reflux were excluded. Patients were randomized into three groups by opening unmarked envelopes indicating the induction regime as follows: PS=propofol 2 mg kg^{-1} and succinylcholine 1 mg kg^{-1}; PR 2=propofol 2 mg kg^{-1} and remifentanil 2 $\mu g\ kg^{-1}$; and PR 4=propofol 2 mg kg^{-1} and remifentanil 4 $\mu g\ kg^{-1}$. No patients were prescribed sedative premedication.

Intravenous access was established, but no fluids were given. Mean arterial pressure (MAP), heart rate (HR), oxygen saturation and end-tidal carbon dioxide ($F\text{E}'_{CO_2}$) were monitored during induction using the Datex Cardiocap. Patients were not preoxygenated, but received oxygen from the end of a Bain system held 5–10 cm caudal to the chin. In group PS, propofol 2 mg kg^{-1} was given over 60 s followed immediately by succinylcholine 1 mg kg^{-1}. In groups PR 2 and PR 4, propofol 2 mg kg^{-1} was followed immediately by remifentanil 2 or 4 $\mu g\ kg^{-1}$, with each drug administered over 30 s. After induction, mask ventilation

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was initiated with 2% sevoflurane in 50% nitrous oxide in oxygen at a total flow of 8 litres min^{-1} and continued in group PS until fasciculation had ceased, and for 30 s in both remifentanil groups. At this point an experienced, blinded anaesthetist took over airway control and attempted tracheal intubation of the patient. During laryngoscopy, each patient was assessed for five variables: jaw mobility; mask ventilation; vocal cord visibility; vocal cord position; and patient movement during intubation. The criteria used for ranking these variables are shown in Table 1.

Following intubation, patients were hand ventilated with a Bain breathing system at five breaths per minute. If $F\text{E}'_{\text{CO}_2}$ levels reached 8 kPa in any patient, ventilation was increased to prevent any further rise. Duration of apnoea was recorded in patients as the period from the beginning of the propofol injection until the first recognizable breath. If spontaneous respiration had not resumed within 15 min (so as not to delay operating time), this time was recorded as the duration of apnoea.

Data were analysed using one-way analysis of variance with Tukey's multiple comparisons (age, weight, duration of apnoea and MAP changes between groups), the paired *t*-test (MAP and HR changes within groups) and the Kruskal–Wallis test with Dunn's multiple comparisons (intubation scores). A value of $P<0.05$ was considered statistically significant.

We studied 17 patients in group PS, 20 in group PR 4 and 23 in group PR 2. One patient in group PR 4 was an unexpected difficult intubation and was withdrawn from the study. Patients in all three groups were similar in age and weight. Mean (SD, range) patient age in groups PS, PR 4 and PR 2 were 44 (15, 18–65) yr, 40 (13, 18–61) yr and 39 (11, 18–62) yr, respectively. Mean patient weight in groups PS, PR 4 and PR 2 were 75 (10, 49–92) kg, 71 (12, 50–94) kg and 76 (15, 55–100) kg, respectively. All subjects in the study were successfully intubated except for two, both in group PR2. In one of these patients vocal cord relaxation was insufficient to allow passage of a tracheal tube, and purposeful movement continued following induction in another. Subsequently, both patients were intubated following the administration of atracurium 0.5 mg kg^{-1}. Scores in the three groups, for each of the five intubation characteristics graded in the study are shown in Fig. 1.

While there were no differences between groups for the intubation characteristic scores of jaw mobility ($P>0.05$), ease of mask ventilation ($P>0.05$) or vocal cord visibility ($P>0.05$), significant differences were found between groups for the characteristics of vocal cord position ($P<0.05$) and movement during intubation ($P<0.001$). Although multiple comparisons demonstrated no significant differences between pairs of groups for vocal cord position ($P>0.05$), movement during intubation was found to be significantly more likely in group PR 2 than in either of the other groups ($P<0.05$). Mask ventilation was described as 'difficult' in one patient in group PR 2 and 'impossible' in

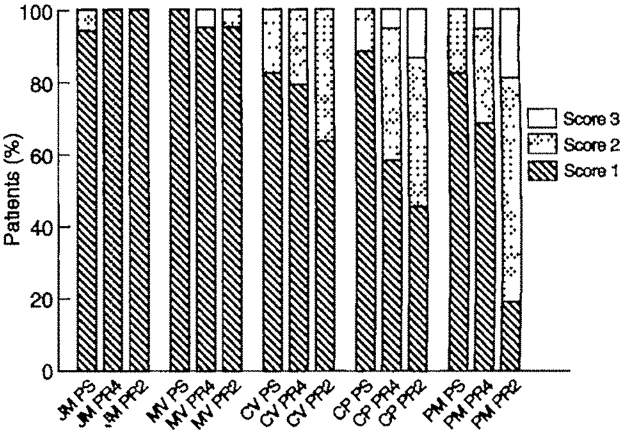

Fig 1 Percentage of patients in groups and the scores attained for each of five intubation characteristics Groups: PS=propofol 2 mg kg^{-1} and succinylcholine 1 mg kg^{-1}; PR4=propofol 2 mg kg^{-1} and remifentanil 4 µg kg^{-1}, and PR2=propofol 2 mg kg^{-1} and remifentanil 2 µg kg^{-1} Intubation characteristics: JM, jaw mobility; MV, mask ventilation; CV, vocal cord visibility; CP, vocal cord position, PM, patient movement

Table 1 Intubating conditions scoring system

Intubation characteristic	**Criteria**	**Score**
Jaw mobility	Jaw mobile	1
	Jaw partly mobile	2
	Jaw immobile	3
Mask ventilation	Mask ventilation easy	1
	Mask ventilation difficult	2
	Mask ventilation impossible	3
Vocal cord visibility	Vocal cords and arytenoids completely visible	1
	Vocal cords and arytenoids partly visible	2
	Vocal cords or arytenoids not seen	3
Vocal cord position	Vocal cords open	1
	Vocal cords mid-position	2
	Vocal cords closed	3
Patient movement	No movement during intubation	1
	One or two coughs during intubation	2
	Persistent coughing or purposeful movement	3

one patient in group PR 4, but neither subject experienced oxygen desaturation, and both were successfully intubated.

Baseline preinduction values of MAP and HR were similar in all three groups ($P>0.05$). Postinduction MAP values decreased from baseline in groups PR 2, PR 4 and PS by 21% ($P<0.0001$), 28% ($P<0.0001$) and 8% ($P>0.05$), respectively. While the difference in post-induction MAP values between groups PR2 and PR4 was not significant ($P>0.05$), post-induction MAP values were significantly lower in both remifentanil groups compared with group PS ($P<0.001$). Values of post-induction HR decreased from baseline in groups PR 2 and PR 4 by 14% ($P<0.01$) and 19% ($P<0.001$), and increased in group PS by 15% ($P<0.01$). One patient in group PR 4, whose heart rate fell to 35 beats min^{-1}, was treated with glycopyrrolate 500 µg. The mean (SD) times, recorded from the beginning of the propofol injection until the first recognizable breath, were 6.0 (0.9) min in group PS, 9.3 (2.6) min in group PR 2 and 12.8 (2.9) min in group PR 4 ($P<0.001$ between all groups).

Comment

Our study has demonstrated that in healthy adults, with normal airway anatomy, a combination of propofol 2 mg kg^{-1} and remifentanil 2 or 4 µg kg^{-1} produces dose-dependent intubating conditions which at the higher remifentanil dose are similar to those produced with succinylcholine 1 mg kg^{-1}. Unfortunately, using a sufficiently high dose of remifentanil to consistently ensure optimum intubating conditions is not without problem. We found significant, dose-related cardiovascular depression associated with the use of a large dose of remifentanil. These levels of hypotension were well tolerated by the subjects in our study, but how they might be tolerated in those less healthy is unproven. High doses of potent opioids are also well recognized to cause muscle rigidity, and in this respect remifentanil is no exception.[5] In our study, two patients receiving remifentanil were difficult to hand ventilate, and this difficulty may well have been due to opioid-induced rigidity.

For an opioid to replace succinylcholine in a rapid sequence induction it should provide optimum intubating conditions, and also allow a rapid return of spontaneous respiration and airway reflexes. Although we demonstrated that patients intubated following remifentanil 4 µg kg^{-1} and succinylcholine 1 mg kg^{-1} had similar intubating conditions, the mean duration of apnoea was more than twice as long in the remifentanil group (12.8 *vs* 6.0 min in the succinylcholine group). The period of apnoea, following a sufficient dose of remifentanil to ensure optimum intubating conditions, would be unacceptable in rapid sequence induction should intubation fail. Although the opioid antagonist, naloxone, could be administered in these circumstances, the degree to which it might lessen apnoea is as yet undetermined.

Our study indicates a role for remifentanil and propofol as an effective method of tracheal intubation. We hope our described technique will be considered an alternative to the use of neuromuscular blocking drugs for procedures requiring tracheal intubation but not muscle relaxation during surgery, and in situations where the use of neuromuscular blocking agents is contraindicated.

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British Journal of Anaesthesia 85 (4): 626–8 (2000)

CASE REPORTS

Two cases of difficult intubation managed by a handmade device†

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The cuffed pharyngeal tube (CPT) is a hand-made device designed to maintain upper airway patency during anaesthesia. Two cases of difficult intubation managed successfully using the new device are described. Insertion was easily achieved at the first attempt in each case. The incisor–tip distance of the CPT is 14 cm and the cuff is inflated with 60 ml of air in an average adult. *Br J Anaesth* 2000 **85**: 626–8

Keywords: equipment, cuffed pharyngeal tube CPT

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The cuffed pharyngeal tube (CPT) was made in 1998 as an alternative to the laryngeal mask airway (LMA*) and cuffed oropharyngeal airway (COPA). It has a simple design and its components can be found in every hospital. A circular band, 7 cm in length, is taken from the wrist portion of a hypoallergenic surgical glove. This will form the new cuff of a 9 mm tracheal tube, the original cuff of which needs first to be ruptured. The new cuff is positioned over the original one and the upper and lower ends are secured with silk ties. This new cuff has a capacity of approximately 70 ml and is inflated via the original pilot tube. A mark is made 14 cm from the tube tip to indicate approximately how far the tube should be inserted (Fig. 1). After midline insertion, the cuff of the modified tube lies in the proximal hypopharynx with its lower margin at the level of the epiglottis and the distal tip passing into the laryngopharynx for 3 cm. Cuff distension is predominantly anterior, i.e. it actively elevates the base of the tongue and lifts the epiglottis by traction.[1–4]

Case 1

A 46-year-old, 116 kg sportsman and body-builder (Fig. 2) came to the operating theatre for hand surgery. Physical examination and blood chemistry were normal. He had a history of a difficult intubation during a previous anaesthetic. The airway was evaluated as Mallampati class 4.[5] His consent for use of the new device was obtained. After the appropriate monitoring had been established, anaesthesia was induced with midazolam 5 mg, diazepam 5 mg (plus 1% Xylocaine 2 ml), fentanyl 150 µg, morphine 8 mg, thiopental 300 + 200 mg and gallamine 40 + 40 mg i.v. Halothane (1.5%), nitrous oxide 2 litre min^{-1} and oxygen 3 litre min^{-1} were then administered with a mask-airway.

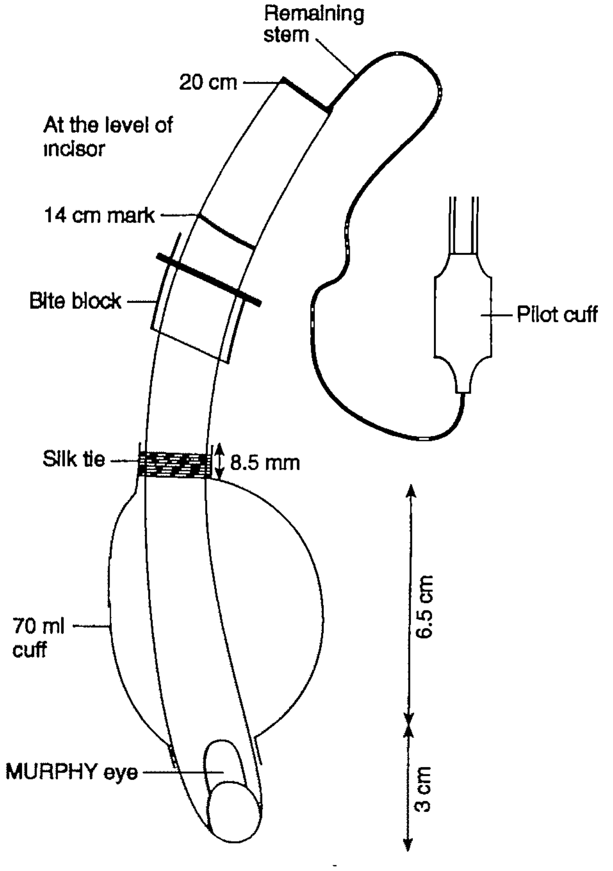

Fig 1 Sketch of the CPT. Note that the cuff distends predominantly from the anterior aspect of the CPT. The bite block is cut from a 10 ml syringe.

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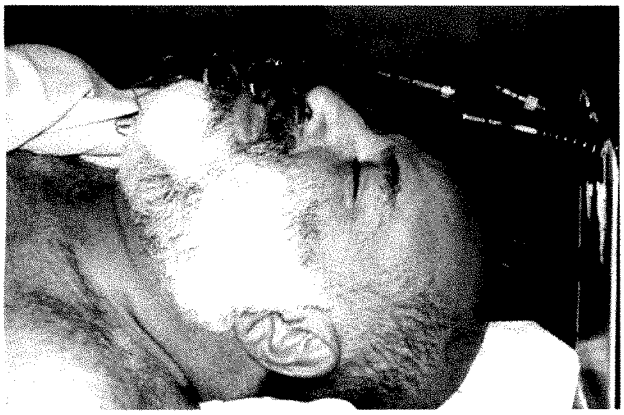

Fig 2 Patient 1 with CPT inserted. Note the technique of fixing the CPT and the shape of the aluminium holder for the corrugated tubes 20 cm above the table surface.

Manual ventilation was difficult because the patient had a bushy beard.

The jaw was completely immobile and head extension was impossible. Thus, the laryngeal structures could not be seen with a laryngoscope. The new airway device was inserted to a depth of 16 cm and the cuff inflated with 80 ml of air. Placement of the device was facilitated by the use of a laryngoscope. The device provided a clear airway and the cuff was outlined with 70 ml of dilute Urographine dye (Fig. 3). Fibre-optic inspection via the CPT lumen confirmed the tip to be just above the laryngeal inlet.

Ventilation was assisted initially, but after 10 min spontaneous respiration returned and the patient was maintained on 0.9% halothane, nitrous oxide 2 litre min^{-1} and oxygen 2 litre min^{-1}. Apart from the arterial pressure and pulse rate, which showed a small rise of short duration after cuff inflation, observations remained within normal limits. Surgery took 1.5 h, after which the cuff of the CPT was deflated while the patient was waking; the CPT was tolerated well. The patient made an uneventful recovery and had no sore throat after the operation.

Case 2

A 34-year-old, 70 kg man was brought to the operating theatre for cervical fusion. His physical examination and laboratory results were within normal limits but he was maintained in halo cervical traction because of fractured vertebrae (Fig. 4).

After attachment of routine monitoring equipment, anaesthesia was induced with fentanyl 150 μg, midazolam 3 mg, thiopental 300 mg and succinylcholine 100 mg. Laryngoscopy was difficult despite a further dose of neuromuscular blocking agent (pancuronium 6 mg) and several attempts at laryngoscopy, using different types of tracheal tubes. However, a CPT was eventually passed easily into the hypopharynx to 14 cm. This provided a good airway after cuff inflation with 60 ml of air. The patient was maintained on positive-pressure ventilation by hand and subsequently attached to a ventilator. Anaesthesia was maintained with 1% halothane in nitrous oxide 2 litre min^{-1} and oxygen 3 litre min^{-1}. The operation for fusion of the fifth cervical vertebra took 1 h.

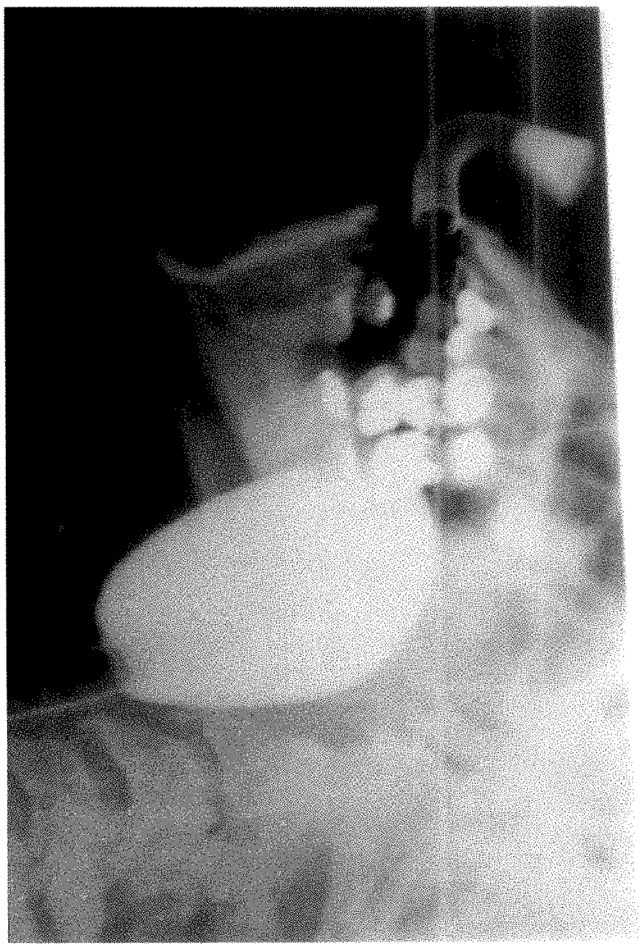

Fig 3 Patient 1. Seventy millilitres of diluted Urographine has been injected into the cuff. Note the horizontal position of the cuff in the proximal hypopharynx at the level of C2–C3.

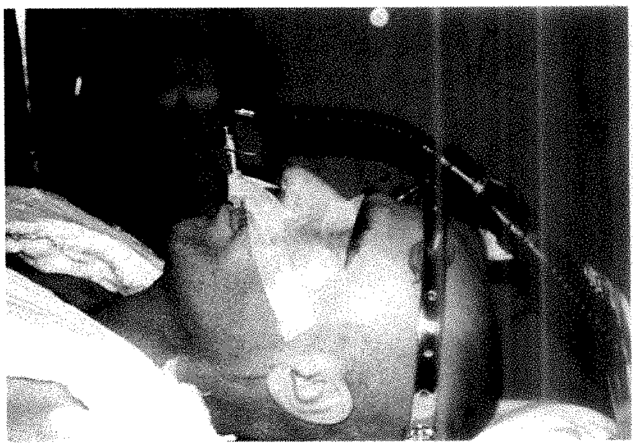

Fig 4 Patient with halo cervical traction. Tracheal intubation was not possible but a CPT was inserted easily.

After reversal of residual neuromuscular block, the patient was woken, and he made an uneventful recovery with no apparent untoward effects.

Discussion

Many techniques and lots of instruments have been designed to overcome the problem of the difficult airway and/or difficult intubation, but they are often either too complicated, too costly or unavailable, especially in poor parts of the world.[6 7] In 1998, a hand-made device was produced to address this problem.

The CPT has now been used in a further 16 cases of difficult airway, and in each case a clear airway was obtained easily and rapidly at the first attempt. The device has proved to be well tolerated and is not easily displaced. Laryngoscopy, though not essential, is recommended, because it locates the epiglottis and facilitates insertion of the device.

When a difficult airway is expected, spontaneous respiration should be maintained but anaesthesia should be deep enough to allow gentle insertion and to prevent rejection of the tube after the cuff has been inflated. Many patients refuse inhalation induction with halothane, and the alternative practice in my institution is a technique based on the use of increasing amounts of analgesics (similar to the principle of pre-emptive analgesia).[8]

A benzodiazepine and small doses of thiopental and a neuromuscular blocking drug are given, while trying to maintain spontaneous respiration with halothane. The addition of small non-apnoeic doses of a neuromuscular blocking agent (e.g. atracurium 10 + 10 mg) facilitates intubation and reduces the likelihood of CPT rejection after the cuff has been inflated. The large dose of neuromuscular blocking agent used in the second patient was inappropriate, but this case is included because it demonstrates the successful use of the CPT in the presence of full muscle relaxation.

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Use of nitric oxide for decompensated right ventricular failure and circulatory shock after cardiac arrest

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We describe a case of peri-operative cardiac arrest, severe right ventricular failure and pulmonary hypertension in a 60-yr-old woman with interstitial pulmonary fibrosis. Inhaled nitric oxide therapy rapidly improved arterial oxygenation and haemodynamic variables, allowing recovery and weaning from mechanical ventilation. Subsequently, the patient was discharged from the cardiac intensive care unit.

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Inhaled nitric oxide (iNO) is widely used in intensive care units in the UK as a powerful selective dilator of pulmonary blood vessels. It has been used to treat pulmonary hypertension in a number of situations such as after paediatric cardiac surgery,[1] implantation of left ventricular assist devices,[2] pulmonary embolectomy,[3] lung transplantation[4] and protamine-induced pulmonary hypertension.[5] Oxygenation in acute respiratory distress syndrome may be improved by reducing ventilation/perfusion mismatch.[6]

Inhaled nitric oxide improves right ventricular function by selective pulmonary vasodilation, which in turn improves left ventricular filling, cardiac output and systemic arterial pressure.[7]

We report the use of iNO as a life-saving measure in a patient with pulmonary fibrosis who had a cardiac arrest after a pulmonary biopsy under general anaesthesia.

Case history

A 60-yr-old woman was scheduled for video-assisted lung biopsy to establish a histological diagnosis of lung pathology. She had a 3.5 yr history of increasing shortness of breath, which had become acutely worse in the 10 weeks before admission. She was unable to walk more than a few yards and was oxygen dependent. She had smoked 30 cigarettes a day for 30 yr and had stopped smoking 13 yr before admission. Her past medical history included a history of thrombocytaemia, which had been treated with hydroxyurea, and this was suggested as a possible cause of the pulmonary fibrosis. Therapy on admission was salbutamol and steroid inhalers, hydroxyurea, frusemide and oxygen.

Blood gas analysis at this time showed that the pH was 7.52, Pa_{O_2} 8.0 kPa, Pa_{CO_2} 3.5 kPa, HCO_3^- 21.2 mmol litre^{-1} and Sa_{O_2} 93% on a fractional inspired oxygen concentration (FI_{O_2}) of 0.24. Pulmonary function tests showed an FEV_1 of 1.31 litres and FVC of 2.59 litres. The FEV_1/FVC ratio was 0.51.

An ECG showed a sinus tachycardia with a rate of 108 beats min^{-1}, right axis deviation and right atrial and ventricular enlargement. Cardiomegaly and enlarged pulmonary arteries consistent with pulmonary artery hypertension were present on a computerized tomography scan of the thorax. The lung fields were abnormal, with increased interstitial markings throughout.

Pre-operative transthoracic echocardiography showed right ventricular enlargement with impaired function, pulmonary hypertension (systolic pulmonary artery pressure 40 mm Hg), moderate to severe tricuspid regurgitation and a small left ventricle with preserved function. Urea, electrolytes and full blood count were normal.

Before induction of anaesthesia, intravenous access was obtained and an arterial cannula was inserted into the left radial artery. After pre-oxygenation, propofol and remifentanil were used for induction and maintenance of anaesthesia. Arterial pressure was 95/56 mm Hg, heart rate 88 beats

Table 1 Cardiorespiratory and inotrope parameters against time of starting iNO. [iNO]=inhaled nitric oxide concentration. Pa_{O_2}=arterial partial pressure of oxygen; FI_{O_2}=fractional inspired concentration of oxygen, Sa_{O_2}=arterial haemoglobin saturation; SIMV=synchronized intermittent mandatory ventilation, BIPAP=biphasic intermittent positive airway pressure, CPAP=continuous positive airway pressure

	Time after starting nitric oxide (min)					
	–30	15	120	240	480	600
[iNO], ppm	0	4	4	10	9	0
Pa_{O_2}/FI_{O_2}, mm Hg	88	150	201	201	181	123
Mean arterial pressure, mm Hg	55	68	65	62	67	64
Central venous pressure, mm Hg	25	12	11	15	8	12
Norepinephrine, µg kg^{-1} min^{-1}	0.4	0.4	0.13	0.13	0.13	0.13
Epinephrine, µg kg^{-1} min^{-1}	0.2	0.2	0.2	0.2	0.23	0.32
Milrinone, µg kg^{-1} min^{-1}	1.2	1.2	0.66	0.66	0.66	0.66
pH	7.19	7.23	7.29	7.37	7.34	7.40
Sa_{O_2} (%)	91	99.3	98.8	100	98.5	94.6
Ventilatory mode	SIMV	BIPAP	ASB	ASB	mask CPAP	Face mask

min^{-1} and oxygen saturation (Sp_{O_2}) 99–100%. Vecuronium 10 mg was given at induction to facilitate tracheal intubation with a 37FG left-sided double lumen tube. After induction of anaesthesia, a right internal jugular venous catheter and thoracic epidural ($T_{7/8}$ level) were placed uneventfully. A total of 10 ml of 0.25% bupivacaine was injected through the epidural catheter. At this time the arterial pressure was 80/50 mm Hg and heart rate 94 beats min^{-1}. The epidural was not used again after this.

After induction and intra-operatively there was a slow but sustained decrease in arterial pressure to 60/25 mm Hg, the heart rate increased to 120 beats min^{-1} in sinus rhythm and central venous pressure (CVP) was increased, at 25 mm Hg. The hypotension did not respond to doses of epinephrine (25 μg in total) and infusion (0.1–0.2 μg kg^{-1} min^{-1}) or methoxamine (2 mg in total). Sp_{O_2} remained at 99% with an FI_{O_2} of 0.5 in air. During lung biopsy the patient developed progressive hypotension and hypoxia, particularly during one-lung anaesthesia. This proved difficult to treat despite increasing the epinephrine infusion, ventilation with 100% oxygen and the use of PEEP (5 cm H_2O) and CPAP (5 cm H_2O) on the dependent and nondependent lung.

On return to two-lung ventilation the saturation improved sufficiently to consider extubation (Sp_{O_2} 97%). However following reversal of residual neuromuscular blockade, before the removal of the tracheal tube the patient suffered an electromechanical dissociation cardiac arrest.

After 20 min of advanced CPR (including the venesection of 1 litre of blood), spontaneous cardiac output returned. We then attempted to pass a pulmonary artery catheter balloon via the right subclavian vein but this could not be advanced beyond the right ventricle. At this time the arterial pressure was 75/35 mm Hg, CVP 35 mm Hg and right ventricular pressure 90/10 mm Hg.

Arterial blood gases showed severe hypoxaemia with Pa_{O_2} 4.0 kPa, Pa_{CO_2} 6.7 kPa, pH 7.32, with an FI_{O_2} of 1.0 and positive pressure ventilation. The patient was already receiving an epinephrine infusion (0.2 μg kg^{-1} min^{-1}); she was transferred to the Cardiac Intensive Care Unit (CICU).

On arrival in the CICU, arterial pressure was 70/30 mm Hg, heart rate 100 beats min^{-1} and regular, CVP 28 mm Hg and right ventricular pressure 75/10 mm Hg. Inotropic support at this time consisted of epinephrine (0.2 μg kg^{-1} min^{-1}), norepinephrine (0.4 μg kg^{-1} min^{-1}) and milrinone (1.2 μg kg^{-1} min^{-1}) infusions. Transthoracic echocardiography showed a grossly dilated right heart (right atrium 6.9 cm) with reduced right ventricular function, reversed septal motion and a small compromised left ventricle with preserved function. There was severe tricuspid regurgitation and an estimated pulmonary artery pressure of 65 mm Hg.

As the patient was *in extremis*, a decision was made to start iNO as a life-saving measure. During the 45 min it took to set up the iNO circuit, the patient remained profoundly shocked, oxygen dependent and unresponsive to changes in inotropic support.

Inhaled nitric oxide (British Oxygen Company, Special Gases Division, Guildford, UK) at a concentration of 4 parts per million (ppm) was started using a nitric oxide delivery system (NOdomo, Drager, Germany) through the ventilator (Evita 4, Drager, Germany). This machine delivers the nitric oxide into the inspiratory limb of the breathing circuit, the volume delivered being in proportion to the inspiratory limb gas flow.

Within 10 min of commencing iNO, haemodynamic and gas exchange status improved rapidly. Norepinephrine and milrinone requirements were reduced to 0.13 μg kg^{-1} min^{-1} and 0.66 μg kg^{-1} min^{-1}, respectively, and the FI_{O_2} was decreased to 0.6. The patient's condition stabilized and weaning from mechanical ventilation was started. The patient progressed to face mask oxygen after 10 h, extubation occurring 5 h after beginning iNO. After the tracheal tube was removed, iNO was continued, using a facial CPAP mask, through the Evita 4 ventilator for a further 4 h. After discontinuing iNO there was some deterioration in gas exchange, but it was not sufficient to warrant restarting it (Table 1).

The nitrogen dioxide concentration did not exceed 0.1 ppm and methaemoglobin concentrations were <0.5% throughout the treatment with iNO.

Haemodiafiltration was instituted on the second day after surgery because the patient developed acute tubular necrosis; it was continued until day 6 of her CICU stay. During this time her inotropic requirements decreased and all inotropes were stopped on day 5. After 7 days the patient was transferred to the High Dependency Unit and she left hospital 2 days later. Lung biopsy showed cryptogenic fibrosing alveolitis and the patient is now awaiting heart/lung transplant.

Discussion

We report the use of iNO in treatment of right heart failure after cardiac arrest. To our knowledge this is the first successful reported use of iNO after cardiac arrest.

Anaesthesia in patients suffering from pulmonary hypertension is difficult, particularly if the patients are to undergo procedures which require one-lung anaesthesia, when hypoxic vasoconstriction in the nondependent lung causes the pulmonary vascular resistance (PVR) to increase more than with two-lung ventilation.

We chose to use a total intravenous anaesthetic technique with a thoracic epidural for this patient. Propofol infusions minimize the ventilation/perfusion mismatch that occurs with one-lung anaesthesia.[8] Thoracic epidural blockade appears to be the technique of choice for analgesia after thoracotomy.[9] Although our patient was only undergoing thoracoscopy, we considered epidural analgesia essential to prevent postoperative hypoventilation and avoid ventilatory support. Although thorascopic surgery is considered less traumatic than thoracotomy, a recent study found moderate or even severe pain scores after minor thorascopic procedures and a decrease in FEV_1 of >50%.[10] However, the technique we used could have contributed to the systemic hypotension seen in our patient because propofol, remifentanil and epidural blockade can all have this effect.

In patients with systemic sclerosis and pulmonary hypertension, exhaled nitric oxide concentrations are lower than those in patients with systemic sclerosis who do not have pulmonary hypertension.[11] It is likely that the same would occur in pulmonary fibrosis. This is supported by the demonstration that, in a patient with severe pulmonary fibrosis, hypoxia and pulmonary hypertension, iNO treatment reduced pulmonary vascular resistance considerably, increased cardiac output and improved oxygenation. The use of intravenous prostacyclin (PGE1) in the same patient resulted in arterial oxygen desaturation and increased dyspnoea.[12] Yoshida and colleagues[13] also found that iNO treatment can decrease pulmonary artery pressure in patients suffering from pulmonary fibrosis. However no improvement in arterial oxygenation was demonstrated whilst breathing room air. If, however, 1 litre min^{-1} of oxygen was then breathed during the iNO treatment, there was a further decrease in pulmonary artery pressure and a significant improvement in arterial oxygenation compared with oxygen therapy alone.

These findings suggest that iNO will benefit patients with pulmonary fibrosis who have hypoxia associated with pulmonary hypertension. Our patient had right ventricular failure because of the high pulmonary vascular resistance. The flow of blood to the left atrium and ventricle was insufficient to maintain an acceptable systemic blood pressure. All these haemodynamic problems rapidly improved when iNO reduced the pulmonary vascular resistance. iNO may be valuable in patients with pulmonary fibrosis and pulmonary hypertension who are undergoing surgery.

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Complete recovery of consciousness in a patient with decorticate rigidity following cardiac arrest after thoracic epidural injection

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A 46-yr-old man with dysaesthesia (burning sensation) following herpes zoster in the left upper chest region was treated with a single thoracic (T2/T3) epidural injection (1.0% lidocaine 3 ml+0.125% bupivacaine 3 ml) as an outpatient. Twenty minutes after the injection, a nurse noticed the patient to be unconscious with dilated pupils, apnoea and cardiac arrest. Following immediate cardiopulmonary resuscitation, the patient was treated with an i.v. infusion of thiamylal sodium 2–4 mg kg^{-1} h^{-1} and his lungs were mechanically ventilated. When the patient developed a characteristic decorticate posture, mild hypothermia (oesophageal temperature, 33–34°C) was induced. On the 17th day of this treatment, after rewarming (35.5°C) and discontinuation of the barbiturate, the patient responded to command. Weaning from the ventilator was successful on the 18th day. About 4 months after the incident, the patient was discharged with no apparent mental or motor disturbances. We suggest that mild hypothermia with barbiturate therapy may have contributed to the successful outcome in this case. *Br J Anaesth* 2000; **85**: 632–4

Keywords: anaesthetic techniques, thoracic epidural; complications, cardiac arrest; complications, hypothermia

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Cervical, thoracic and lumbar epidural injections are common out-patient procedures in pain clinics.[1 2] Unintentional dural puncture, and if unnoticed, total spinal block is a recognized complication of these techniques. Prompt respiratory and circulatory support lead to complete recovery.[3] We report a case of unsuspected total spinal block presenting with cardiac arrest following thoracic epidural block in our out-patient pain clinic. The outcome was good even though there was evidence of severe neurological damage following cardiopulmonary resuscitation.

Case report

A 46-yr-old man with pain (burning sensation) in the T2–T3 dermatomes following herpes zoster was receiving single thoracic epidural injections (1% lidocaine 3 ml+0.125% bupivacaine 3 ml) three times a week in our out-patient clinic. Previous treatment had included a 1-month course of regular local anaesthetic injection through an indwelling epidural catheter as in in-patient. A trial of epidural spinal cord stimulation at the T2–3 level with a catheter electrode was unsuccessful. About 20 min after an apparently uncomplicated epidural block at the level of T2/T3 in the out-patient clinic, a nurse found the patient to be unconscious with widely dilated pupils, apnoea and cardiac arrest. Immediate cardio-pulmonary resuscitation was performed including intracardiac injection of epinephrine 1 mg. The patient was resuscitated and within 5 min of being found had an arterial pressure of 120/90 mm Hg and heart rate of 90 beats min^{-1}, but remained unconscious.

The patient was admitted to our intensive care unit (ICU) ~30 min following resuscitation and his lungs were mechanically ventilated with PEEP (5 cm H_2O). Blood gas analysis showed pHa 7.462, Pa_{CO_2} 33.8 mm Hg, Pa_{O_2} 128 mm Hg, base excess –1.4 mMol $litre^{-1}$ at FI_{O_2} 0.4. An i.v. infusion of thiamylal sodium 2–4 mg kg^{-1} h^{-1} was started. Muscle rigidity continued to develop despite the barbiturate therapy, and eventually a characteristic decorticate posture developed. The tendon reflexes of all limbs were highly accentuated. The pupillary light reflexes, tested 2–3 h after transiently stopping the infusion of thiamylal, were absent. The EEG showed no electrical activity, although auditory brainstem responses were present with normal interpeak latencies and delayed peak latencies. Some small respiratory movements were observed and the cerebral circulatory index (CCI, cerebral blood flow divided

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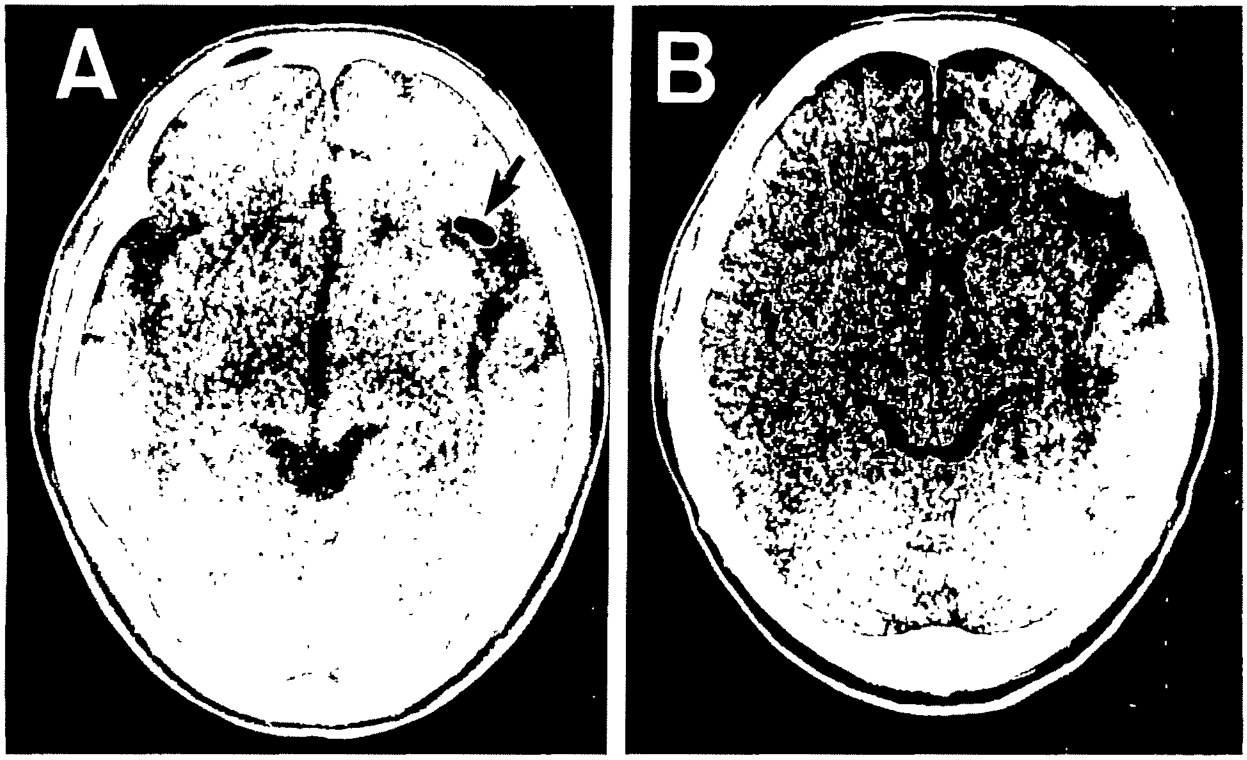

Fig 1 Computed tomography of the patient on the second (A) and fifth (B) days after ICU admission Note diffuse oedema particularly in the occipital area in (A) and a slight atrophic picture in (B) An arrow indicates air bubbles in the third ventricle

by cerebral metabolic rate of oxygen which is the inverse of the arterovenous oxygen content difference) was 16 at an oesophageal temperature of 37.2°C.

Computed tomography (CT) on the second day after ICU admission demonstrated an oedematous area in the brain, mainly in the occipital cortex and air in the ventricles which was thought to have been introduced during the epidural injection (Fig. 1). Glycerol (100 mg) and dexamethasone (0.5 mg) were infused i.v. over 2 h, before mild hypothermia (oesophageal temperature 33–34°C) was induced by surface cooling. Within 3 days of this treatment, a repeat CT scan showed that the air bubbles in the cerebral ventricles had disappeared and the oedematous shadow was smaller (Fig. 1). On the sixth day after admission to ICU, the decorticate rigidity had decreased but hyperreflexia persisted. The pupils responded to light, and θ band waves in the EEG were observed at this time. On the 17th day after ICU admission, the infusion of the thiamylal was tapered and rewarming of the body was started. When the oesophageal temperature was 35.5°C, the patient nodded in response to command. Weaning from the ventilator was successful after several trials on the 18th day after ICU admission.

After endotracheal extubation, the patient opened his eyes and was able to weakly grip a hand, although he still showed accentuated tendon reflexes, retrograde amnesia, disorientation and difficulty in walking. After the patient was transferred to the general ward, these neurological signs resolved gradually. Cerebral blood flow scintigram (^{123}I-IMP brain SPECT) showed low perfusion areas in the frontal cortex, left temporal cortex, bilateral basal ganglia and hippocampus. Rehabilitation therapy for the weakness and rigidity of the upper and lower limbs resulted, 4 months after his admission to our hospital, in the patient being discharged without recognizable mental or motor disturbance except for a slight dysaesthesia on his toes.

Discussion

We think that this patient developed a total spinal block caused by an accidental dural punction during epidural injection of local anaesthetic This occurred despite the operator following the correct procedures, a negative aspiration test and no apparent untoward effects in the few minutes after the epidural injection. Adhesions of the dura mater and/or narrowing of the epidural space produced by the previous epidural interventions might have contributed to the dural puncture. The air bubbles present in the third ventricle are likely to have been injected with the local anaesthetic into the intrathecal space[2] rather than during the intracardiac injection of epinephrine. Alternatively, a high thoracic epidural block, by blocking cardiac accelerator sympathetic fibres, might have caused the cardiac arrest,[4–6] although baroreflex blockade by high epidural block has been questioned.[7]

There have been previous case reports of the accidental total spinal block and recovery with various neurological disabilities after resuscitation.[4–6 8–14] However, there have been no reports of adult patients who had decorticate rigidity for several days after cardiac arrest and recovered, except in an elderly patient with accidental hypothermia.[15] As our patient had decorticate rigidity and diffuse brain oedema, the clinical outcome seemed desperate at first. However, the CCI was 16–18, suggesting a matching of cerebral blood flow and metabolism even though there was EEG silence.[16]

This case might suggest that intensive treatment with the combined use of mild hypothermia[17] and barbiturate therapy should be tried when there is a decorticate rigidity with profound suppression of brainstem reflexes following cardiopulmonary resuscitation. We used thiamylal instead of thiopental in this case, as thiamylal, which has similar pharmacokinetics to thiopental,[18] was found to be more effective in attenuating the increase in intracellular calcium concentration produced by NMDA receptor activation than thiopental.[19]

This case also demonstrates that patients must be continuously monitored by close observation of respiratory, circulatory as well as neurological signs and symptoms for at least 20 min following epidural injection.

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Phaeochromocytoma diagnosed during labour

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The diagnosis of phaeochromocytoma during pregnancy is rare. We present the management of vaginal delivery in a woman diagnosed with the condition during labour. A Medline search and follow-up of references failed to find any similar report in the last 30 years.

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Keywords: complications, phaeochromocytoma; pregnancy

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Case history

A 34-yr-old, para 1, gravida 2 woman presented for induction of labour at 38 weeks' gestation because of gestational diabetes. Her previous pregnancy had resulted in an uncomplicated vaginal delivery. She had been apparently normotensive throughout this pregnancy. Gestational diabetes was diagnosed at 30 weeks' gestation and required insulin to control it. At 34 weeks' gestation, the woman complained of headaches and was admitted for daycare monitoring of arterial pressure, which revealed no problems. There was no proteinuria. A diagnosis of atypical migraine headaches was made by the physicians who reviewed her.

The woman was admitted for induction of labour. Prostin gel 1 mg was administered *per vaginum*. The following morning, an infusion of 10% dextrose and potassium (10 mmol per 500 ml dextrose) was commenced with an i.v. insulin infusion started at 2 units h^{-1}. Artificial rupture of membranes was performed at 2 cm cervical dilation. An epidural catheter was then sited uneventfully at L3/4 and 10 ml of 0.25% bupivacaine was given. The first epidural top-up was requested 2.5 h later. An anaesthetist was called to check the epidural, because blood-stained aspirate was noted in the catheter. During examination of the catheter, the mother coincidentally became grey and clammy, and complained of a severe throbbing frontal headache. Her arterial pressure, measured non-invasively, was then 220/140 mm Hg. Within 10 min, the patient had recovered and her arterial pressure had returned to normal. She stated that similar headaches had occurred during the previous 3 months, that they lasted 5–120 min and occasionally only stopped after vomiting. Her arterial pressure had never been measured during one of these episodes.

The presence of sudden, severe hypertension and abnormal glucose tolerance led us to a presumptive diagnosis of phaeochromocytoma. The epidural was topped up to T5 using 10 ml of 0.375% bupivacaine. Phentolamine was prepared as a rescue hypotensive agent. With this epidural management, the patient's arterial pressure remained normal, even during contractions, and she had no further symptoms. The cardiotocograph (CTG) also remained normal. After discussion between the obstetricians, anaesthetists and the patient, it was decided to allow a trial of vaginal delivery with a short active second stage of labour. The epidural was topped up every 2 h to maintain good analgesia and sympathetic blockade. The patient began active pushing 4.5 h after the presumptive diagnosis, 1 h after full cervical dilation had been noted. After 10 min of pushing, she became breathless and felt unwell. Her arterial pressure peaked at 240/144 mm Hg but returned to normal when she stopped pushing. The obstetricians performed a ventouse delivery of the baby followed by manual removal of the placenta. A healthy 3.3 kg boy was delivered. The attendant anaesthetist administered intravenous boluses of phentolamine (3 mg total) during delivery, which kept the arterial pressure within normal limits (124/74 to 134/58 mm Hg). After delivery, the mother's arterial pressure remained labile, requiring further boluses of phentolamine (4 mg total). She was transferred to the high dependency unit; invasive monitoring of arterial pressure was initiated and a phentolamine infusion started at 4 mg h^{-1}. After medical review, oral phenoxybenzamine 10 mg tds was commenced.

Investigations 24 h after delivery revealed an increased serum epinephrine concentration of 413 nmol $litre^{-1}$ (normal range 10–93 nmol $litre^{-1}$), which is

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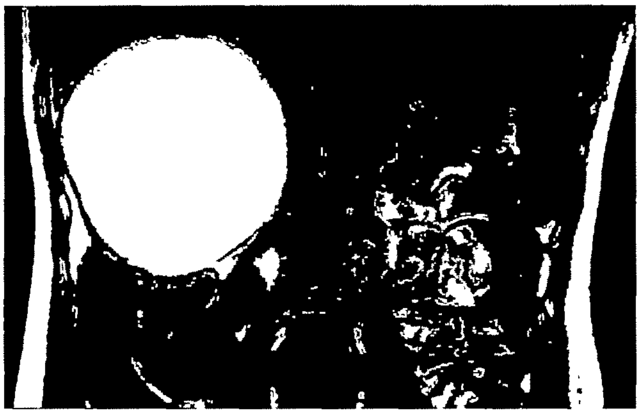

Fig 1 MRI coronal section of the upper abdomen showing right-sided suprarenal mass (12×12 cm) (seen as the large white spherical object) which was found to be a phaeochromocytoma. The vertebrae can be seen in the midline in the lower half of the picture The liver has been displaced cephalad, and is seen immediately above the mass. The kidney (grey, with pale edge below mass), which has been displaced caudally, can be seen between two sections of gas-filled bowel (black)

diagnostic of a phaeochromocytoma. Norepinephrine and dopamine serum concentrations were within the normal range. On days 1, 2 and 3 *post partum*, urine tests showed normetanephrine concentrations of 29.4, 52.5 and 35.5 μmol litre^{-1}, respectively (normal range 0–3 μmol litre^{-1}), and metanephrine concentrations of 2908, 2231 and 3043 μmol litre^{-1}, respectively (normal range 0–2 μmol litre^{-1}). A magnetic resonance imaging (MRI) scan 3 weeks *post partum* revealed a 12 cm cystic mass arising from the right adrenal gland (Fig. 1). The phenoxybenzamine was gradually increased to 10 mg tds and the patient underwent uneventful laparotomy 8 weeks later. A 13×12×9 cm tumour was resected. Histology revealed a cystic lesion with a blood-stained centre and a peripheral adrenal paraganglioma consistent with a phaeochromocytoma. The patient made an uneventful recovery. Complete resection of the tumour was confirmed biochemically.

Discussion

The presence of a phaeochromocytoma during pregnancy and especially during labour exposes the mother and fetus to significant risk of death. Before 1970, there was a reported overall maternal and fetal mortality of 48% and 61%, respectively, in such patients.[1] For cases reported between 1980–1987, this mortality had decreased to 17% and 26%, respectively,[2] but was 33% and 39%, respectively, when the diagnosis was not made before labour. Antenatal diagnosis was made in only 53% of patients in this series (all before labour). The most recent *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom*[3] recorded five deaths caused by phaeochromocytoma, emphasizing that mortalities still occur.

Once the presence of a phaeochromocytoma was suspected, it was decided to maintain epidural analgesia using 0.375% bupivacaine to produce extensive and dense sympathetic blockade without excessive weakness of the legs. The adrenal gland is innervated by sympathetic nerves from T5 to T12. Thus epidural sympathetic blockade across these levels would obtund the neurogenic stimulation of a possible adrenal tumour. An epidural would also provide optimal analgesia, thus reducing catecholamine concentrations further. Deafferentation would ensure optimal placental perfusion, which is particularly important in the presence of a rarer, extra-adrenal tumour. With this management, arterial pressure remained normal in this patient throughout the first stage of labour. Hypertension in response to placement in the lithotomy position has been noted in a patient with an extra-adrenal tumour who received antenatal α and β blockade and an epidural catheter with bolus doses of 0.25% bupivacaine during labour.[4] No comment was made about the height of the epidural block during this case. Our patient had no such problems. The labour progressed uneventfully; invasive monitoring of arterial pressure was deferred as the patient's arterial pressure was controlled and she remained asymptomatic.

There are no previous reports of phaeochromocytoma being diagnosed in labour (from Medline search and follow-up of references), so there is no clear guidance in the literature about the preferred mode of delivery in such patients. The majority of cases not diagnosed antenatally required Caesarean section for fetal distress. Between 1980 and 1987, there were 17 cases reported of women undiagnosed antenatally who survived to delivery.[2] Twelve had Caesarean sections, with eight mothers and 10 babies surviving. Five were delivered vaginally, with four of the mothers and four of the babies surviving. There is thus no suggestion that one mode of delivery is less hazardous than another in this situation. Epidural analgesia allowed the option of vaginal delivery or 'topping up' for Caesarean section.[5–7] In our case, the obstetricians had not anticipated any problems with vaginal delivery. We decided to pursue a vaginal delivery unless hypertension or an abnormal CTG suggested the need for Caesarean section. Phentolamine controlled the patient's arterial pressure during instrumental delivery. We chose this α blocker because of its rapid, titratable effect when given intravenously. It can be given peripherally as a bolus or as an infusion. Phenoxybenzamine and labetolol were other options. Phenoxybenzamine takes up to 1 h to take effect after intravenous administration and needs to be given slowly over 2 h. Labetolol has a longer, less predictable onset time than phentolamine and we preferred to use a pure α blocker, as tachycardia was not a problem in this patient. Both the alternative drugs thus have an unacceptable onset time. The effectiveness of the epidural meant that manual removal of the placenta was uneventful, with no arterial pressure problems.

In summary, we have described the successful management of a multigravida patient with a phaeochromocytoma diagnosed during labour. Optimal management of a pregnant woman with a phaeochromocytoma should include antenatal diagnosis and α and β blockade. Unfortunately, some patients will not be diagnosed before delivery. With extended epidural sympathetic blockade, intravenous α blockade, limitation of pushing during the second stage of labour and close monitoring of arterial pressure, successful vaginal delivery was achieved.

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ABSTRACTS

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*(The name of the author presenting the paper is shown in bold type. *Indicates non-member)*

VERBAL PRESENTATIONS

Matrix metalloproteinase-9 and tumour necrosis factor α during cardiopulmonary bypass: relationship to heparin infusion

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An inflammatory response occurs in patients undergoing cardiac surgery involving cardiopulmonary bypass (CPB), characterized by complement activation and release of tumour necrosis factor α (TNFα). Active TNFα is released following cleavage of an alanine–valine bond, catalysed by proteases including the matrix metalloproteinase (MMP-9). MMP-9, an endopeptidase, is secreted as a pro-enzyme in response to a variety of inflammatory mediators, and degrades extracellular matrix proteins. Pro-MMP-9 is transcriptionally regulated by TNFα and converted to active MMP-9 by plasmin and heparin. The effects of heparin infusion during CBP on MMP-9 and TNFα are unknown.

Circulating MMP-9 concentrations were measured in 20 patients (15 male, five female, median age 61.8 yr) undergoing elective coronary artery bypass grafting involving CPB. Blood samples were obtained before and 10, 30 and 120 min after the start of heparin infusion and placed immediately into ice. After centrifugation, samples were stored at –80°C for subsequent enzyme immunoassay of total MMP-9 and TNFα. Data are expressed as median (range) and were assessed using Friedman with Wilcoxon signed ranks *post hoc* testing for paired data.

TNFα and MMP-9 increased significantly in all patients over time. TNFα had increased by 10 min and a further increase occurred 120 min after heparin infusion. However MMP-9 increased only 120 min after heparin infusion (Fig. 1). These data show that MMP-9 increases during CPB, which has profound implications for the inflammatory response. TNFα increases very soon after the start of heparin infusion, but MMP-9 increase does not occur until later. This suggests that regulation of MMP-9 may not involve heparin and is likely to have little impact on early TNFα release.

Keywords: tumour necrosis factor; metalloproteinase; heparin

Transient hyperaemic response to assess vascular reactivity of the skin: effect of sodium nitroprusside iontophoresis

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Reperfusion hyperaemia has been used to assess skin vascular reactivity.[1] Little is known about the validity and reproducibility of the transient hyperaemic response (THR) in the forearm after release of brief compression of the brachial artery. Our aim was to address these issues.

We studied 10 healthy male adult volunteers. Subjects lay supine with one forearm outstretched and supported. Skin blood flow flux was measured using laser Doppler flowmetry. A custom-made iontophoresis chamber was secured to the skin on the anterior aspect of the distal forearm. Arterial pressure was recorded at 3 min intervals throughout. Skin temperature was measured before and after each set of readings.

After establishing a steady baseline, five THR tests were performed by compressing the brachial artery in the antecubital fossa for 20 s, repeated at 2 min intervals. Sodium nitroprusside (SNP; 2%) was iontophoresed using a current of 100 μA for 240 s to produce vasodilation. The THR test was then repeated three times.

Changes in laser Doppler flux were recorded using a paper chart recorder. Flux was measured in volts. The THR ratio was calculated as flux after release of compression divided by baseline flux before compression. Of the five THRs recorded before SNP, the difference between maximum and minimum THR ratio normalized for mean THR ratio was taken as an index of variability. The mean flow flux and THR ratios before and after SNP were taken for further analysis.

Wilcoxon signed rank test was used to analyse the changes. Mean (range) index of variability for THR ratios was 0.29 (0.10–0.76). After SNP iontophoresis, baseline flux increased and THR was abolished (Table 1).

We conclude that iontophoresis of SNP abolishes THR, suggesting that THR is a valid indicator of vascular reactivity.

Keywords: transient hyperaemic response; vascular reactivity

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Cardiac energy provision in myocardial hypertrophy by fatty acids

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Fatty acids are thought to provide about 70% of the energy requirements of the heart.[1] It is uncertain what proportion is derived from non-esterified fatty acids, and what proportion from

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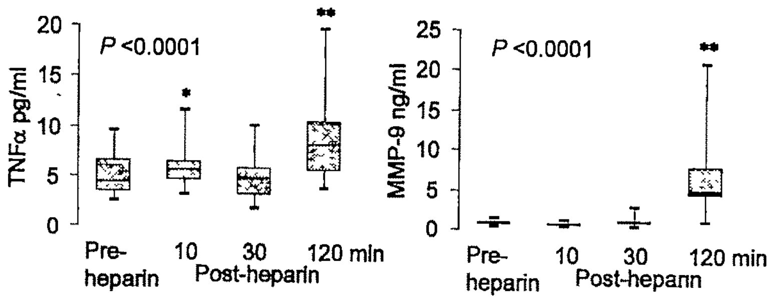

Fig 1 Plasma TNF-α and MMP-9 concentrations in 20 patients undergoing CPB. Box-and-whisker plots show median, 25th and 75th percentiles and full range. *P* value refers to Friedman analysis of variance over time. $*P<0.005$ and $**P<0.0001$ compared with pre-heparin value

Table 1 Effect of sodium nitroprusside (SNP) iontophoresis on transient hyperaemic response (THR). $*P<0.006$ compared with corresponding control value

	Control		After SNP iontophoresis	
	Flow flux	**THR ratio**	**Flow flux**	**THR ratio**
Mean	0.777	1 65	1 844*	1.00*
Range	0 290–1 617	1 00–2 54	0.733–2.917	0.98–1.03

esterified fatty acids (triacylglycerols (TAGs) in the form of lipoproteins, chylomicrons and very-low-density lipoprotein (VLDL)). During cardiac hypertrophy, fatty acid oxidation has been reported to decrease because of decreased cytosolic carnitine content,[2] and exogenous glucose utilization increased with increased glycolysis.[3] We studied the effect of myocardial hypertrophy in the rat heart on energy provision by the major cardiac lipid substrates. Male Wistar rats (125–150 g) had cardiac hypertrophy induced by abdominal suprarenal aortic banding (0.8 mm); at 8 weeks, hearts were removed and perfused in 'working' mode for 60 min. Perfusate was recirculating Krebs–Henseleit buffer supplemented with [^{14}C]glucose, together with [^{3}H]oleate or [^{3}H]triolein in the form of rat VLDL (prepared by rat liver perfusion) or rat chylomicrons (prepared by rat thoracic duct cannulation). Cardiac hydraulic work (cardiac output×developed aortic pressure), and glucose ($^{14}CO_2$ plus $H^{14}CO_3^-$ production) and fatty acid ($^{3}H_2O$ production) oxidation were measured. ATP equivalents were calculated from standard stoichiometry.

Growth and body weights were similar in all groups but hearts from animals with aortic stenosis were significantly heavier, confirming myocardial hypertrophy. Cardiac mechanical performance was similar in all groups when expressed per gram of wet weight of heart (data not shown). The metabolic fate of fatty acids (esterified and non-esterified) was calculated as fatty acid-derived ATP equivalents, as a proportion of ATP derived from glucose oxidation (Fig. 2); aortic stenosis had no significant effect on the proportion of energy derived from lipid or carbohydrate precursors. These results indicate that the rat heart is able to maintain cardiac function even at a relatively late stage of hypertrophy, and this is associated with preservation of the lipid:carbohydrate utilization balance for energetic provision, regardless of the source of the fatty acid moiety.

Keywords: heart, hypertrophy, fatty acid, triacylglycerol

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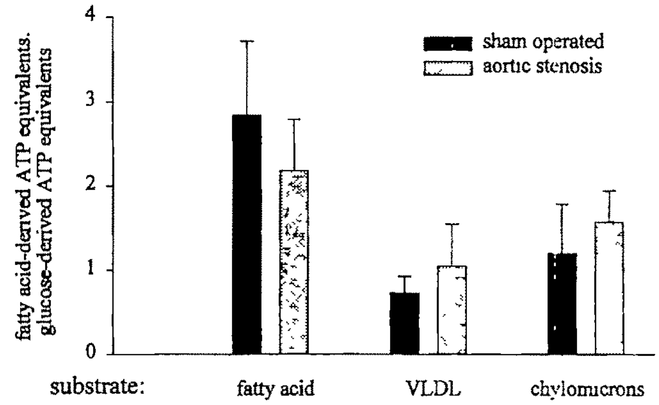

Fig 2 Proportion of ATP derived from fatty acid compared with glucose. Means±SE; $n=6–9$

Glucose, insulin and potassium do not protect the heart during open cardiac surgery

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In 1998 the ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group reported a reduction in mortality when high-dose glucose–insulin–potassium (GIK) was used to treat acute myocardial infarction.[1] The protection afforded by GIK was thought to be based on anaerobic glucose metabolism and provision of ATP energy to the ischaemic heart muscle.[1] Cardiac troponin I (TnI) is a structural protein in cardiac myocytes. TnI measured in peripheral blood provides a sensitive and specific indication of myocardial cell damage.[2] We sought to determine whether GIK has the potential to decrease myocardial damage during cardiac surgery with cardiopulmonary bypass (CPB)

A preliminary prospective, randomized double-blind study of 36 patients undergoing elective coronary artery bypass surgery with intermittent cardioplegia was conducted. Patients received either 5% dextrose (non-GIK) or 50% dextrose with added insulin and potassium (GIK) infusions throughout the operative period. Samples were collected for TnI assay before induction of anaesthesia, after removal of the aortic cross-clamp, and 6 and 12 h after CPB. Cold (6°C) oxygenated blood containing St Thomas' cardioplegia solution was used for myocardial preservation. Statistical analysis was performed using the Mann–Whitney *U*-test.

The groups were well matched for age, ejection fraction and aortic cross-clamp and bypass times ($P>0.05$) In both groups there was an increase in TnI concentrations following CPB. At

Table 2 Median (interquartile range) TnI concentrations (µg litre^{-1}). *Significantly different from baseline concentrations ($P<0.05$), †significantly different from concentrations after cross-clamp ($P<0.05$)

	Baseline	After cross-clamp	6 h after CPB	12 h after CPB
GIK	0.1 (0)	0.8 (0.8)*	2.8 (2.8)†	2.0 (1.0)
Non-GIK	0.1 (0)	0.2 (0.95)*	2.9 (6.55)†	2.0 (6.1)

none of the four time points was there a significant difference in TnI concentrations between the two groups ($P>0.05$) (Table 2).

Keywords: cardiac surgery; glucose

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Thromboelastography in warfarinized patients

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The thromboelastograph (TEG) is used for near-patient haemostatic assessment. There is debate regarding the safety of regional anaesthesia in patients taking anticoagulants.[1 2] Spinal haematoma with neuraxial blockade is rare, but may have devastating consequences. The International normalized ratio (INR) is the accepted test for monitoring the effect of warfarin. There is no consensus about the maximum INR which allows safe performance of regional anaesthesia, with suggested values ranging from a conservative 1.5[1] to a more liberal upper limit of 2.8[2] TEG parameters have not previously been shown to reflect the INR. We evaluated the relationship between tissue factor (TF)- and celite-activated TEG values and the INR in patients taking warfarin.

Blood was taken from 37 patients on warfarin into sodium citrate tubes (ratio 9·1). The INR was measured in the laboratory. Thromboelastography was carried out 30 min after venesection, after recalcification of specimens, using TF and celite as activators. We examined several TEG parameters: *R* and *K* values, which reflect time to initial clot formation, α angle, which corresponds to rate of clot extension, and maximum amplitude, which gives an indication of clot strength. Spearman rank correlation was used to evaluate the relationship between individual parameters and the INR. A multivariate regression model was used to evaluate the independent effects of these variables.

Table 3 shows Spearman rank correlations for individual TEG variables and the INR. There was no significant relationship between the TF or celite maximum amplitudes and the INR. R_{TF} was the most powerful predictor of INR with a coefficient of 0.13 (95% CI 0.09–0.17; $P=0.0001$). This predicts a 0.13 increase in INR for every 1 mm prolongation of R_{TF}. The coefficient of determination of this model, r^2, was 0.58.

The TF-activated TEG supplies valuable information about coagulation in patients taking warfarin. However, no single TEG parameter or combination thereof reliably predicted the INR in individual patients. No effect of warfarin on clot strength could be detected.

Acknowledgements

We thank the Royal College of Anaesthetists and Medicell for their support

Keywords: coagulation, measurement, thromboelastograph; warfarin

Table 3 Spearman rank correlations for individual thromboelastography variables and the INR

Variable	Spearman correlation with INR (95% CI)
R_{TF}	0.79 (0.62–0.88); $P<0.0001$
R_{celite}	0.59 (0.32–0.76); $P<0.0001$
K_{TF}	0.42 (0.12–0.66); $P=0.009$
K_{celite}	0.34 (0.02–0.6); $P=0.04$
α angle for TF	–0.46 (–0.68 to –0.15); $P=0.005$
α angle for celite	–0.32 (–0.58 to –0.01), $P=0.06$

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Flow limitation in expiration during general anaesthesia

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Upper airway collapse is frequent during general anaesthesia, and is usually evident during inspiration.[1] Limitation of flow during expiration has been described in awake individuals with sleep-disordered breathing, and is presumably caused by upper airway collapse.[2] We tested patients during anaesthesia for flow limitation during expiration by applying negative pressure at the mouth.[3]

We recruited 34 patients (mean age 34 yr, range 16–73 yr) from elective gynaecology lists. After induction of anaesthesia we measured flow and pressure at the mask during spontaneous ventilation, using a pneumotachograph, pressure transducer, an A/D converter and Spike 2 software. In the test breaths, approximately –5 cm H_2O was applied to the expiratory pathway during part of expiration and the volume exhaled during this period was compared with that during a corresponding period in a control breath. In 11 subjects we could repeat the measurements after insertion of a laryngeal mask airway.

The expiratory flow increased in most subjects (Fig. 3) The increase in exhaled volume during the application of negative pressure was 22% (13–39) (median, quartile values). In the 11 subjects who had increases in the lowest quartile, four were studied after insertion of a laryngeal mask airway. This did not reverse the limitation.

We conclude that, in contrast to patients with sleep-disordered breathing, expiratory flow limitation is rare in anaesthetized

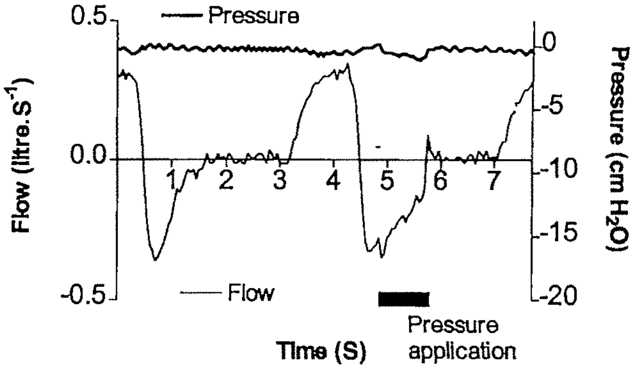

Fig 3 Mask flow and pressure during a control breath and a test breath. During the test breath subatmospheric pressure was applied during expiration.

females, and, when it is found, it appears unlikely to be associated with limitation by events in the upper airway.

Acknowledgement

This study was funded by Edinburgh University (Physiology Honours Project).

Keywords: airway, collapse; flow limitation

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Effects of repeated anaesthesia on central cholinergic function in elderly rats

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Young (6–8 month) Lewis rats were trained on a neurobehavioural task and, after matching for reaction time performance, were allocated randomly to two groups. Rats in the test group (n=15) were deprived of food to 85% of free feeding weight, tested on the behavioural task and anaesthetized with sodium pentobarbital 20 mg kg^{-1} by ip injection. Two days later, the behavioural task was repeated. The sequence was repeated at 6, 8.5, 11, 13.5, 16, 18.5, 21 and 23.5 months of age. A final behavioural test was performed 2 months later. Animals in the control group (n=12) were treated identically except that no anaesthetics were given. After the final test session, the rats were killed and decapitated and the heads were cooled in liquid nitrogen for 8 s. The cortex, hippocampus and striatum were dissected at 4°C and stored at –80°C. Half the tissue was retained in Maastricht for measurement of striatal choline acetyltransferase activity and glial fibrillary acid protein. The results of these assays and the behavioural tests will be reported elsewhere.

The remaining tissue was analysed in Newcastle by autoradiographic assay of [^{3}H]epibatidine and α-[^{125}I]bungarotoxin binding. Quantitative image analysis for both assays was done blinded to test condition with Lynx Image analysis (Applied Imaging) against radioisotope standards, focusing on the regions showing the highest density of binding. Choline acetyltransferase was measured using [^{14}C]acetyl coenzyme A as a substrate. The results are shown in Table 4.

We conclude that repeated anaesthesia in the rat results in a reduction of nicotinic cholinergic receptors in the cerebral cortex at which anaesthetic agents, including barbiturates, are known to have an effect at clinical concentrations. The findings should be replicated but may provide an explanation for postoperative cognitive dysfunction in the elderly.

Acknowledgement

A.B. was supported by the Royal Netherlands Academy of Arts and Sciences.

Keywords: anaesthesia; receptors, cholinergic

Table 4 Effect of anaesthesia on central cholinesic function *$P<0.05$ mean±SD

	Control (n=8)	**Anaesthetized** (n=9)
Choline acetyltransferase activity (nmol h^{-1} mg protein^{-1})		
Cortex	49.8±10.7	56.1±12.05
Hippocampus	62.84±19.4	63.36±16.17
Epibatidine binding (fmol mg^{-1})		
Superior cortex	23.88±10.25	19.48±4.14
Molecular cortex	33.04±12.77	27.15±4.64
Cingulate cortex	39.22±11.67 (n=7)	29.52±9.32
CA 2/3	21.77±7.44	25.73±18.75
Dentate gyrus	15.84±3.71	16.94±5.13
α-Bungarotoxin binding (fmol mg^{-1})		
Superior cortex	8.60±0.83	6.78±0.46*
Molecular cortex	6.06±0.88	5.32±0.69*
Inner cortex	8.21±1.22	7.50±1.08
Cingulate cortex	21.49±9.48	17.05±5.88
Dentate gyrus	27.99±25.69	24.46±10.99

The influence of a single amino acid on etomidate sensitivity at heteromeric $\alpha_1\beta_3\gamma_2$ GABA$_A$ receptors

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At clinically relevant concentrations, many intravenous general anaesthetic agents enhance the action of GABA acting at GABA$_A$ receptors.[1] The interaction of etomidate with this inhibitory receptor is of particular interest as it is dependent upon the subunit composition of the receptor, being selective for receptors containing β_2- or β_3- rather than β_1-subunits. This selectivity is dependent on the nature of a single amino acid (asparagine for β_2 or β_3 and serine for β_1) located in the second transmembrane domain.[2] Mutation of the homologous amino acid within the glycine receptor α_1 subunit suggests that the volume of this residue is inversely correlated with the activity of certain anaesthetics and alcohols.[3] In this study, we compared the actions of etomidate on wild type GABA$_A$ receptors (composed of $\alpha_1\beta_3\gamma_2$ subunits) with their effects on receptors in which asparagine at position 289 of the β_3 subunit was replaced by the smaller amino acids glycine ($\alpha_1\beta_{3N289G}\gamma_2$) or alanine ($\alpha_1\beta_{3N289A}\gamma_2$).

Xenopus laevis oocytes were injected with cRNAs encoding wild-type or mutant subunits and 2–12 days after injection electrical recordings were made at a holding potential of –60 mV using the two-electrode voltage-clamp technique. To investigate the enhancement of agonist-evoked responses by etomidate, a concentration of GABA producing a peak current 10% of the maximum (EC_{10}) was determined for each oocyte. Etomidate was applied for 60 s before co-application with the agonist From such experiments, the anaesthetic E_{max} (the amplitude of the GABA-evoked response in the presence of a maximally effective concentration of anaesthetic expressed as a percentage of the maximal effect of GABA) and the EC_{50} (the concentration of anaesthetic producing half-maximal enhancement) were determined. All observations are based on a minimum of three oocytes.

The enhancement of GABA-evoked currents by etomidate was slightly reduced by replacing the asparagine 289 residue with alanine (wild-type: EC_{50} 4±0.1 μM, E_{max} 81±5%; $\alpha_1\beta_{3N289A}\gamma_2$: EC_{50} 5±3 μM, E_{max} 68±3%). By contrast, the positive allosteric effects of etomidate were dramatically reduced at the $\alpha_1\beta_{3N289G}\gamma_2$ receptor (EC_{50} 14±0.1 μM, E_{max} 24±2%). Furthermore, the replacement of asparagine by alanine resulted in an approximately seven-fold decrease in sensitivity to GABA (EC_{50} 40±3 μM) in comparison with the wild-type receptor (EC_{50} 6.1±0.9 μM). These results suggest that asparagine 289 may contribute to an anaesthetic-binding site or play a pivotal role in receptor transduction.

Acknowledgements

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Keywords: intravenous anaestheitcs, etomidate; receptors, $GABA_A$

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Modulation of the $GABA_A$ receptor by the intravenous general anaesthetic Org 25435

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Org 25435 (2,6-dimethoxyphenyl-4-methylphenyl-2′-*N*-*bis*(2′-methoxyethyl)aminobutyrate–HBr) is a water-soluble general anaesthetic that is undergoing preliminary clinical studies.[1,2] Many general anaesthetics enhance the actions of GABA acting at the $GABA_A$ receptor and this may contribute to their central depressant effects.[3] Here, we have characterized by electrophysiological recordings the interaction of Org 25435 with human $GABA_A$ receptors and compared this effect with those of propofol, etomidate and pentobarbitone.

cRNAs encoding the human $GABA_A$ receptor subunits α_1, β_3 and γ_{2L} were injected into the cytoplasm of *Xenopus laevis* oocytes. $GABA_A$ receptor-mediated currents were recorded 2–12 days later from oocytes voltage-clamped at −60 mV. A concentration of GABA producing a peak current 10% of the maximum (EC_{10}) was found and the EC_{50} (the concentration of anaesthetic producing half-maximal enhancement of this response) and E_{max} (the maximal effect of the anaesthetic expressed as a percentage of the maximum response to GABA) were determined. In the absence of GABA, all anaesthetics tested induced a picrotoxin-sensitive inward current (a GABA-mimetic effect) and the EC_{50} and E_{max} for this effect (or the maximal effect produced in the absence of a clear maximal effect at the highest concentration tested) were also determined.

Org 25435 produced a concentration-dependent potentiation of GABA-evoked currents with an EC_{50} approximately 2.5-fold greater than that of propofol and etomidate and 4.6-fold less than that of pentobarbitone. However, both the maximal modulatory and mimetic effects of Org 25435 were much less than those produced by the other anaesthetics (Table 5). In conclusion, Org 25435 is a potent allosteric modulator of the $GABA_A$ receptor and this action may contribute to the behavioural effects of this anaesthetic.

Keywords: intravenous anaesthetics; receptors, $GABA_A$

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The effect of xenon on transmission along the somatosensory pathway in rats anaesthetized with urethane or inactin

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It is possible that the investigation of anaesthetic action in animals could be biased by the basal anaesthetic required for the necessary surgical preparation of the animals. Accordingly the action of xenon has been investigated in rats anaesthetized with urethane, a long-acting carbamate, at 1.25 g kg^{-1} or inactin, a long-acting barbiturate, at 167 mg kg^{-1}). Respiration, ECG, electrocorticogram, evoked cortical responses and single cortical cell responses were recorded. The animals were allowed to breathe oxygen spontaneously for at least 1 h before xenon administration (10, 20, 40, 60 and 80%) to obviate the problem of xenon/nitrogen exchange.

The results are shown in Table 6. Eighty per cent xenon caused a small but statistically significant ($P<0.05$; paired *t*-test) decrease in heart rate and respiratory rate with both anaesthetic agents. The relative power in the low-frequency (δ; 0.5–3.5 Hz) and high-frequency (β, 14.0–30.0 Hz) bands of the electrocorticogram were significantly altered in urethane-anaesthetized rats but not in inactin-anaesthetized animals. Inhalation of 80% xenon in animals anaesthetized with either anaesthetic gave a significant increase in the latency and significant decreases in the amplitudes of the first positive and first negative waves of the cortical responses evoked by supramaximal stimulation of the forepaw. Single cells recorded from cortical layers IV and V, in response to electrical stimulation of the forepaw, showed similar increases in median latency and decreases in their probability of discharge with both anaesthetic agents.

Table 5 GADA modulator and GADA mimetic activity of ORG 25435, Propofol, Etomidate and Pentobarbitone. ND=not determined

	GABA modulation		GABA mimetic	
	EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
Org 25435 (*n*=4)	10±1	47±4	ND	5±1
Propofol (*n*=7)	4±0.1	89±7	50±2	52±6
Etomidate (*n*= 3)	4±0.2	81±5	ND	ND
Pentobarbitone (*n*=6)	46±3	84±4	407±23	57±3

Table 6 Comparison of urethane and Inactin anaestheaia for the data on single-cell responses in cortical layers IV and V, * indicates significant differences from control levels

	Urethane anaesthesia			Inactin anaesthesia		
	n	Control	80% xenon	*n*	Control	80% xenon
Heart rate, beats min^{-1} (mean (SD))	12	454.7±40.1	403.4±46.5	14	442.1±18.7	414.5±24.5
Respiration, breaths min^{-1} (mean (SD))	12	90.5±13.0	87.7±18.5	14	72.4±11.3	67.0±9.5
Relative power						
δ bands	6	21.7±1.0	36.4±3.4	7	7.8±5.1	8.7±6.3
β bands	6	36.4±3.4	27.0±14.5	7	51.3±8.9	57.0±11.6
Cortical response evoked by supramaximal stimulation of forepaw Latency (ms)	12	3.59±0.27	4.69±0.38	14	3.61±0.22	4.44±0.31
Amplitude of first positive wave (%)	12	100±10.9%	62.9±22.5	14	100±10.8%	62.4±12.1
Amplitude of first negative wave (%)	12	100±48.8%	13.4±8.1	14	100±23.2%	27.8±20.4
Median latency (ms)						
cortical layer IV	6	0±0.21	0.49±0.68	13	0±0.21	0.65±0.71
cortical layer V	10	0±0.35	3.1±1.47*	8	0±0.43	1.40±1.64*
Probability of discharge						
cortical layer IV		100±8.9%	20.5±16.5*		100±17.8%	25.1±22.1*
cortical layer V		100±7.3%	24.6±22.5*		100±16.5%	41.6±23.0*

Table 7 A60 Thromboelastogin measurement @ 60 mins MA = maximum amplitude

	Normal/abnormal DWBCLT		A60/MA (SD)		Blood transfused (interquartile range)
	Before	After	Before	After	
MB	4/12	9/7	92.9 (3.1)	97.0 (2.6)	6 (5–9)
Control	12/4	10/6	83.9 (27.2)	96.3 (5.1)	4 (1–6)

These data indicate that the changes seen in the responses of the somatosensory pathway to 80% xenon are identical for both anaesthetics used. They also show that changes in the evoked cortical responses are a much more robust indicator of change in anaesthetic depth than is the change in the power spectrum of the electrocorticogram.

Acknowledgement

Grateful thanks are given to BOC for donating the xenon used in this study.

Keywords: xenon; somatosensory pathway

Does methylene blue inhibit fibrinolysis following reperfusion injury?

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The dye methylene blue (MB) has been used both as an antioxidant and as a nitric oxide blocking agent. We have previously reported its effect in attenuating haemodynamic changes of ischaemia reperfusion syndrome in human orthotopic liver transplantation (OLT). This was mediated both by inhibition of cGMP and reduced levels of nitric oxide.[1] It might therefore be expected to influence clot stability and fibrinolysis following reperfusion in OLT. We have investigated this hypothesis.

We studied 32 patients undergoing OLT, powered on previous thromboelastographic data. All patients received a standardized anaesthetic. Patients were allocated randomly to receive MB 1.5 mg kg^{-1} or an equivalent volume of normal saline intravenously by rapid bolus 1 min before graft reperfusion. Blood samples were taken immediately before and 1 h after reperfusion. Dynamic coagulation variables were assessed by thromboelastography (TEG).[2] We also measured dilute whole blood clot lysis time (DWBCLT) as a more sensitive index of clot lysis.[3] Patient characteristics and transfusion requirements were recorded.

There were no major differences between treated and control patients in TEG variables or DWBCLT after reperfusion. However, there was a large chance baseline difference in DWBCLT between treatment and control patients. When results were analysed correcting for this, improvement in fibrinolysis (DWBCLT) was greatest in the treatment group (P=0.009) (Table 7).

We have failed to show a conclusive reduction in fibrinolysis or improved clot stability in patients receiving MB.

Keywords: methylene blue; ischaemia–reperfusion injury; orthotopic liver transplantation; fibrinolysis

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Tetrahydrobiopterin concentrations during septic shock

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Nitric oxide synthase has a requirement for tetrahydrobiopterin for catalytic activity. Although circulating nitrate concentrations increase in patients with septic shock, concentrations are highly dependent on renal function. In a rat model of sepsis, changes in circulating tetrahydrobiopterin concentrations preceded increases in nitrate and correlated with arterial pressure. We measured

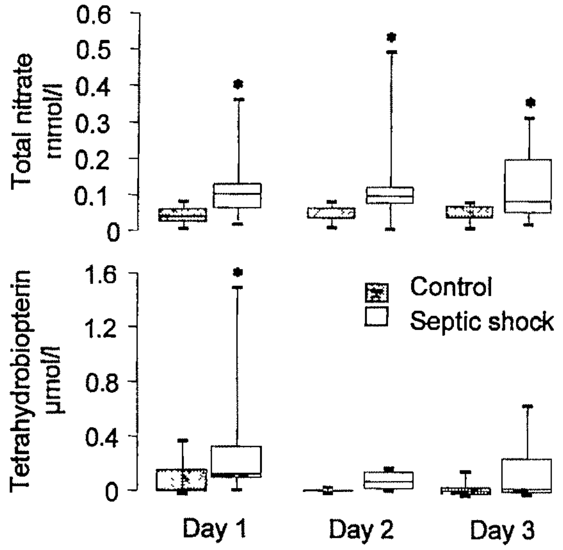

Fig 4 Plasma total nitrate and tetrahydrobiopterin concentrations in 10 patients with septic shock and 10 non-septic controls Box-and-whisker plots show median, 25th and 75th percentiles and full range. $^*P<0.05$ compared with non-septic controls.

plasma tetrahydrobiopterin as an early biochemical marker of septic shock, compared with plasma nitrate.

Blood samples were obtained on day 1, and 24 and 48 h later from 10 patients with septic shock and 10 non-infected control patients. Plasma total nitrate was measured using Greiss reagent after reduction of nitrite to nitrate on a copper-coated cadmium column. Tetrahydrobiopterin concentrations were measured using HPLC after selective oxidation with iodine. Data are expressed as median (range) and were analysed using Friedman analysis of variance or Mann–Whitney *U*-test as appropriate.

The APACHE II score was 22 (13–27) in patients with septic shock and 25 (7–28) in the non-septic control group. Total nitrate concentration was significantly higher in patients with septic shock than in non-septic critically ill controls on all days but did not change with time. Tetrahydrobiopterin concentrations were highest in the patients with septic shock on day 1 only (Fig. 4). Seven patients with septic shock and none of the controls had renal failure. Nitrate was 129.0 (18.5–417.7) μmol litre^{-1} and tetrahydrobiopterin was 1.2 (0.8–14.9) μmol litre^{-1} in patients with renal failure, compared with 41.8 (3.3–150.1) and 0.16 (0–5.8) μmol litre^{-1}, respectively, in those without renal failure. Nitrate correlated with tetrahydrobiopterin concentrations on day 1 ($P=0.002$).

In patients with septic shock, both plasma tetrahydrobiopterin and total nitrate concentrations were higher than in critically ill non-septic patients, early after admission to the intensive care unit. Both tetrahydrobiopterin and nitrate are increased mainly in patients with renal failure. Tetrahydrobiopterin is difficult to measure and offers little advantage over nitrate measurement.

Acknowledgement

A. L was a 1999 Anaesthetic Research Society Vacation Scholar.

Keywords· tetrahydrobiopterin; sepsis

Serum acetaminophen (paracetamol) concentrations in adult volunteers after rectal administration

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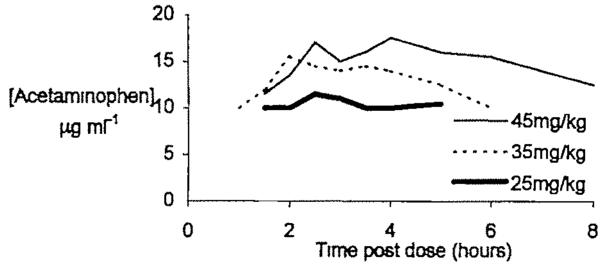

Fig 5 Median serum concentrations of acetaminophen after rectal administration of 25, 35 or 45 mg kg^{-1}.

Acetaminophen is usually given in adults at a dose of 10–20 mg kg^{-1} orally or rectally. Work in children suggests that doses of 40 mg kg^{-1} are needed when this drug is given by the rectal route.[1] We have investigated the dose of rectal acetaminophen needed to achieve serum concentrations within the accepted therapeutic range of 10–20 μg ml^{-1} in adults.

Ten healthy volunteers received increasing doses of rectal acetaminophen (15, 25, 35 and 45 mg kg^{-1}) on separate occasions at least 48 h apart. The hospital pharmacy manufactured acetaminophen suppositories with the exact dose required for each volunteer. On each day of the study, an intravenous cannula was put in place and a baseline blood sample taken. The suppository (witpsol base) was then self-administered and serum acetaminophen concentrations were measured every half hour until 4 h then hourly until 8 h after administration (Cambridge Life Sciences enzymatic assay; lower limit of detection 10 μg ml^{-1}).

Plots of the median serum concentrations after administration of the three highest doses are shown in Fig 5. Median (range) peak concentrations were 12.5 (<10–18), 16.5 (10–23) and 20 (17–25) μg ml^{-1} after 25, 35 and 45 mg kg^{-1}, respectively. Doses of 35–45 mg kg^{-1} of rectal acetaminophen are needed to achieve sustained therapeutic serum concentrations in healthy adult volunteers. These doses provided serum concentrations >10 mg ml^{-1} for median time periods of 5.5 h (35 mg kg^{-1}) and 6 h (45 mg kg^{-1}). The highest serum concentration measured was 25 μg ml^{-1}, which is well below the accepted toxic concentration of 120 μg ml^{-1}. Our results have confirmed recent work by Beck *et al.*[2]

Acknowledgement

We thank Torbay Hospital Special Medical Projects and Research Fund for financial support.

Keywords: acetaminophen, pharmacokinetics; rectal administration

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The influence of polymorphisms in the interleukin 10 (IL-10) gene on lipopolysaccharide-stimulated IL-10 release: interim analysis

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Differential interleukin 10 (IL-10) expression is implicated in autoimmunity and critical illness, and genetic variation in IL-10

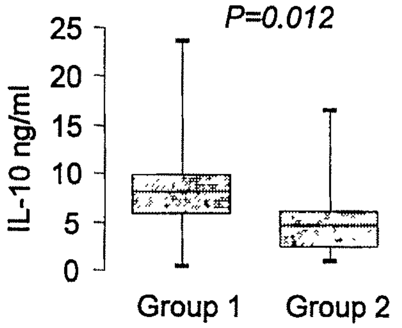

Fig 6 Stimulated IL-10 concentrations in subjects with IL-10R allele 1 plus IL-10 1* allele 3 (group 1, n=19) and those without these alleles (group 2, n=25) Box-and-whisker plots show median, 25th and 75th percentiles and range. P value refers to Mann–Whitney U-test.

responses may determine the outcome of critical illness. Two dinucleotide repeat polymorphisms have been identified in the IL-10 gene, one in the promoter region (termed IL-10G) and one in the 5′ flanking region (IL-10R). Several single nucleotide substitutions (point mutations) have also been described. The contribution of these polymorphisms to IL-10 production is not known. Power calculations based on published data for IL-10R allele frequency suggested that 102 subjects were required. We present an interim analysis.

Blood samples were obtained from 44 healthy volunteers (20 male; median (range) age 25 (21–46) yr). Genomic DNA was extracted using a BACC3 DNA isolation kit Restriction fragment length polymorphism (RFLP) analysis was used to identify point mutations at base pairs –1082 (termed IL-10 1*) and –627 (IL-10 3*). Specific PCR primers were used to amplify dinucleotide repeats and alleles were identified using a DNA fragment size analyser. Whole blood IL-10 production was measured after 24 h incubation with lipopolysaccharide 1 μg ml^{-1} using enzyme immunoassay. IL-10 concentrations were related to combined allele frequency. Data were analysed using the Mann–Whitney U-test.

IL-10R analysis yielded four alleles and IL-10G analysis nine alleles. RFLP analysis gave two alleles for IL-10 1* and two for IL-10 3*. IL-10 concentrations initially appeared very variable (range 0.26–23.5 ng ml^{-1}). However, allele frequency analysis for IL-10 1* and IL-10R polymorphic markers showed an association between IL-10 release and allele number such that subjects (n= 25) possessing the IL-10 1* allele 1 together with IL-10R allele 3 had a median IL-10 concentration of 8.52 (0.26–23.5) ng ml^{-1} compared with 5.40 (1.35–16.80) ng ml^{-1} in subjects (n=19) without these alleles (P=0.012; Fig. 6). Allele frequencies of the IL-10G dinucleotide repeat and the IL-10 3* single nucleotide substitution were not correlated with IL-10 production.

Power re-analysis based on IL-10R alone showed that 131 subjects are required to show an association between IL-10R allele frequency and IL-10 concentrations. However, when combined with IL-10 1* allele frequency, we have shown an association with IL-10 production in 44 subjects. These data reveal that IL-10 release in response to an inflammatory stimulus is related to a polymorphic genetic marker. Further studies to investigate the use of this marker in determining IL-10 response in critically ill patients are now warranted.

Acknowledgements

We are grateful to the British Journal of Anaesthesia/Royal College of Anaesthetists for financial support.

Keywords: interleukin-10; polymorphism; immunity

Effect of endotoxin on the utilization of fatty acid and triacylglycerol by rat macrophages

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The hypertriglyceridaemia resulting from sepsis arises through a tissue-specific decrease in the clearance of very-low-density lipoprotein-triacylglycerol (VLDL–TAG) by the enzyme lipoprotein lipase and through increased hepatic VLDL synthesis.[1] VLDL produced during endotoxaemia is structurally distinct from normal VLDL. We proposed that this abnormal septic/endotoxic VLDL (eVLDL) provides substrate for biological systems during stress: VLDL-TAG supports increased cardiac mechanical work and is an efficient myocardial substrate.[2] The immune system also has increased activity during endotoxaemia and is a candidate target tissue for eVLDL in addition to the heart. VLDL–[^{3}H]triolein was produced by rat liver perfusion.[3] To produce eVLDL, rats were treated with lipopolysaccharide (LPS) (from *Escherichia coli* 05:55) (500 μg kg^{-1} ip). Rat R2 macrophages were cultured in RPMI 1640 medium supplemented with glutamine (2 mM), fetal calf serum (10% v/v) and bovine serum albumin (0.5% w/v). VLDL, eVLDL or oleate (0.3 mM) was added with or without LPS (1000 ng ml^{-1}) and the cells were incubated for a further 48 h. Total utilization of VLDL–TAG or oleate was the sum of released tritiated water (oxidation) and the residual tritiated intracellular lipids stored within mechanically recovered macrophages.

Oleate utilization showed a linear increase throughout the experiment; LPS significantly increased oleate utilization at 24 h, leading to a 2.5-fold increase in total utilization by 48 h (Fig 7A). Utilization of control VLDL–TAG represented about 75% of the oleate used by macrophages. Addition of LPS to control VLDL incubations almost completely abolished VLDL–TAG utilization. However, macrophages incubated with eVLDL and LPS utilized significant amounts of eVLDL–TAG when compared with similar groups incubated with cVLDL and LPS (Fig. 7B). These results indicate that LPS increased free fatty acid utilization but abolished utilization of VLDL–TAG By contrast, incubation with eVLDL and LPS restored some VLDL–TAG utilization, although this remained less than in experiments without LPS. It is postulated that eVLDL may function as a substrate for the macrophage during sepsis, enabling limited TAG utilization than would otherwise be abolished by the endotoxin.

Keywords: macrophage; fatty acid; VLDL; triacylglycerol; sepsis

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Propofol infusions for sedation in paediatric intensive care: pharmacokinetics in neonates and children

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The use of propofol infusions in paediatric intensive care is limited, partly because of concerns about serious cardiovascular and metabolic complications of (as yet) unknown cause.[1 2] There

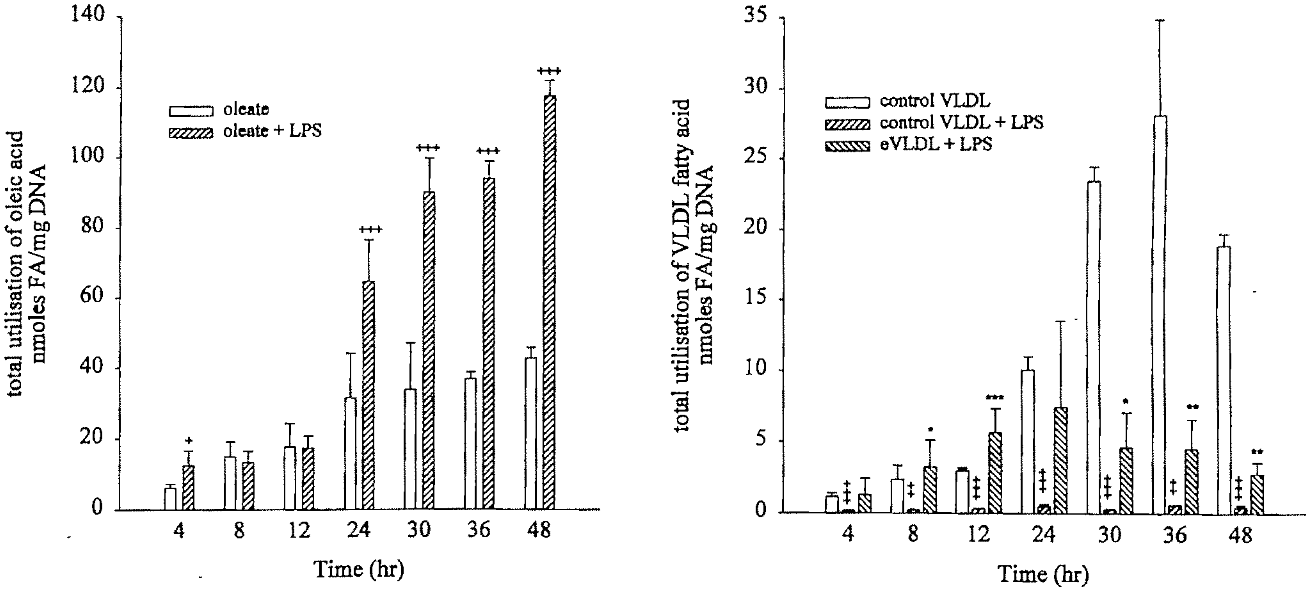

Fig 7 Mean±SD utilization of (A) oleic acid and (B) VLDL fatty acid by cultured R2 cells (n=5) +, ++ and +++, effect of LPS; *, ** and ***, control VLDL versus eVLDL.

Table 8 Kinetic data

Pharmacokinetic parameter	Range
Steady-state plasma concentration (μg litre^{-1})	0.81–5.38
Post-infusion AUC (μg min mL^{-1})	110–8118
Elimination half-life α (min)	8.1–85.0
Elimination half-life β (h)	4.5–463.8
Clearance (ml min^{-1})	36.7–1013.7
Clearance (litres kg^{-1} min^{-1})	0.010–0.123
V_{ss} (litres kg^{-1})	1.74–706.5
MRT (min)	367–39911

is no published information on the pharmacokinetics of propofol in the critically ill infant.

We studied 21 children aged 1 week to 12 yr who required ventilation and sedation in the paediatric intensive care unit; 17 were postoperative cardiac surgery patients and four were admitted for medical reasons. The children were sedated with 2% propofol for ≤28 h, according to the expected duration of mechanical ventilation, in combination with morphine 20–40 μg kg^{-1} h^{-1}. Propofol was infused at 4 mg kg^{-1} h^{-1} increasing to 6 mg kg^{-1} h^{-1} if the child showed signs of distress. Propofol 4 mg kg^{-1} h^{-1} achieved adequate sedation in 17/20 patients. The propofol infusion rate was reduced in two patients because of hypotension. Blood lipid concentrations were measured before and after infusion and did not increase in any child. One child was withdrawn due to persistent hypotension and lactic acidosis but this occurred prior to propofol administration.

Blood samples for measurement of propofol concentrations were taken during the infusion and for 24 h afterwards. Propofol was extracted from whole blood[3] and quantified by HPLC.[4] Kinetic data were fitted to a two-compartment model and are summarized in Table 8.

The calculated propofol clearance in critically ill children was in good agreement with data obtained from previous studies on children with a range of illnesses (cited in ref. 5), but elimination half life, V_{ss} and MRT were considerably larger than previously reported.

Keywords: propofol, pharmacokinetics; children

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The effect of diclofenac on interleukins 6 and 10 in patients undergoing major surgery

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Prostaglandins increase cAMP and promote a T-helper cell 2 (Th2) response, through increased release of Th2 cytokines (interleukins (IL) -6 and -10) whilst interferon γ and IL-12 are decreased. Diclofenac inhibits cyclooxygenase activity and, hence, prostaglandin production and should promote Th1 responses. In a randomized, double blind, placebo-controlled study we investigated the effect of perioperative administration of diclofenac on circulating concentrations of IL-6 and IL-10 in patients undergoing major urological surgery.

Patients were allocated randomly to receive either diclofenac (50 mg 8 hourly the day before surgery and 75 mg i.m. 12 hourly on the day of surgery; n=12) or placebo (n=12). Anaesthetic technique and postoperative epidural analgesia were the same in both groups. Study groups were similar with respect to age, gender, body weight, fentanyl consumption, blood transfusion and duration of surgery. IL-6 and IL-10 were measured before surgery and 30 min and 2, 6, 12 and 24 h after skin incision using in-house enzyme immunoassays.

One patient from each group was withdrawn from the study.

Concentrations of IL-6 and IL-10 increased over time, peaking at 12 h and 6 h, respectively. The IL-6 concentration was significantly higher ($P<0.05$) at 2, 6 12 and 24 h than basal levels in the placebo group and at 6, 12 and 24 h in the diclofenac group (Fig. 8). The IL-10 concentration was greater ($P<0.05$) at 6, 12 and 24 h than basal levels in both groups. At 12 h, IL-6 concentrations were significantly lower in those patients who had received diclofenac than in those who had received placebo ($P=0.014$, Fig. 8). IL-10 concentrations tended to be higher in the diclofenac group at 6 h ($P=0.061$). Diclofenac was also associated with significantly less pyrexia, lower leucocyte counts and lower C-reactive protein concentrations. These preliminary data have shown that major surgery is accompanied by marked increases in IL-6 and IL-10 concentrations. Perioperative diclofenac treatment was accompanied by a reduction in peak concentrations of IL-6, a tendency to increased peak concentrations of IL-10 and a subdued postoperative inflammatory response. Diclofenac is known to decrease concentrations of prostaglandins, which in turn leads to a reduction in cAMP concentration and should promote Th1 responses. In our study, decreases in IL-6 concentration were preceded by increases in IL-10 concentration. The mechanism of the increase in IL-10 concentration remains unclear.

Keywords: interleukins; diclofenac

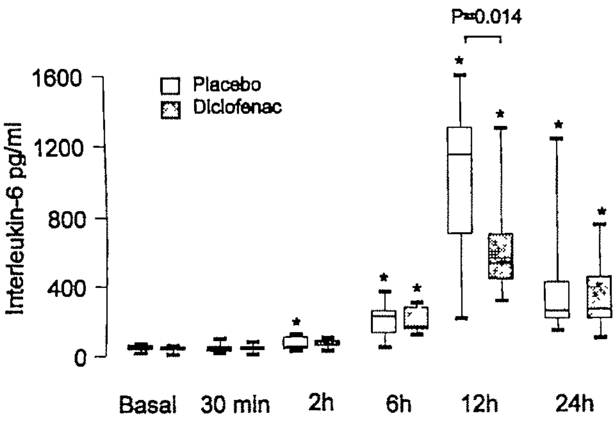

Fig 8 IL-6 concentrations in surgical patients following randomization to diclofenac ($n=11$) or placebo ($n=11$) Box-and-whisker plots show median, 25th and 75th percentiles and range. *Greater than before surgery (basal) ($P<0.05$).

Magnetic resonance images of the thoracic epidural space after epidural catheters, heparin and cardiac surgery

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We have performed magnetic resonance image (MRI) scans of the thoracic epidural space in patients who have received thoracic epidural analgesia to treat pain after cardiac surgery involving cardiopulmonary bypass. The risk of formation of clinically significant epidural haematoma after use of epidural catheters has been estimated at one in 150,000.[1] Use of heparin i.v may increase this figure. Series of patients have received epidural catheters and heparin without damage to the thoracic spine measured by clinical examination.[2] MRI shows bleeding best by detection of methaemoglobin on days 4–7 after a bleed.[3] This study was designed to use MRI scans to detect epidural bleeding in patients not expected to demonstrate clinical neurological signs.

Thoracic epidural catheters were inserted at the T3/4 or T4/5 interspace before induction of anaesthesia; 4–5 cm of catheter was left in the epidural space. Heparin 300 IU kg^{-1} i.v was given before cardiopulmonary bypass at 32°C. Epidural analgesia was obtained using infusion of clonidine and bupivacaine, then patient-controlled bupivacaine and fentanyl. Epidural catheters were removed on the second or third day after surgery. MRI scans were performed on the fourth day after surgery.

Eleven patients, mean (range) age 65 (50–73) yr, mean (SD) weight 79 (6) kg, mean (SD) height 175 (9) cm had epidural catheters inserted 137 (range 104–335) min before heparin i.v; MRI using T1 and T2 weighted scans and 4 mm cuts was performed 39 h 42 min (24 h) (range 16–99.5 h) after removing the epidural catheter. The scan of one patient was performed on the seventh day after surgery. There was no evidence of blood in the epidural space on any scan. No patient reported neurological symptoms or demonstrated neurological signs on clinical examination.

Incidental MRI findings were: cervical spondylosis ($n=8$), lumbar disc space degeneration ($n=6$), thoracic spondylosis ($n=4$), lumbar disc protrusions (3), early cervical spinal stenosis ($n=1$), cervical disc space degeneration ($n=1$), dural ectasia ($n=1$) and sacral arachnoid cysts ($n=1$).

On days 4–7 one would expect to see increased intensity specks

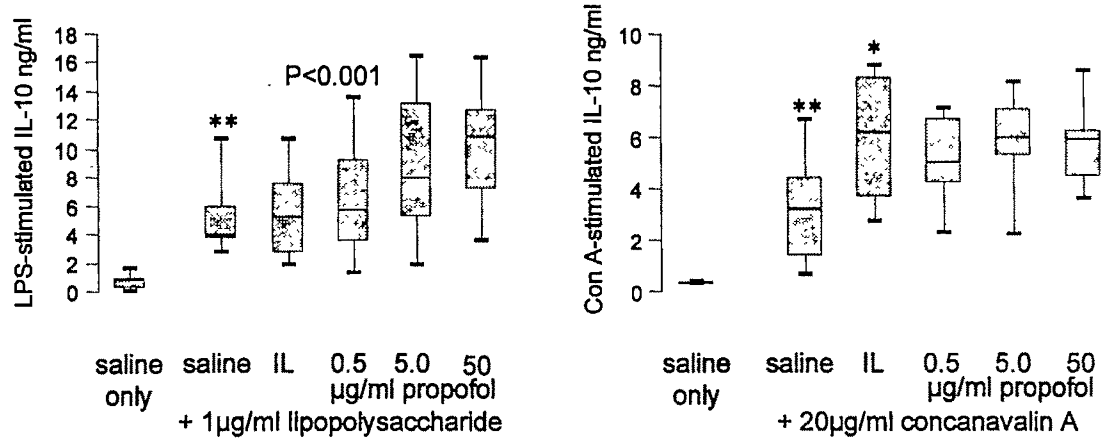

Fig 9 IL-10 concentrations in blood cultured with LPS or Con A, plus Intralipid (IL) or propofol. Box-and-whisker plots show median, 25th and 75th percentiles and range. P value refers to analysis of variance *$P<0.05$ compared with saline + Con A **$P<0.0001$ compared with blood cultured without LPS or Con A.

on T1 weighted MRI if bleeding had occurred. These result from oxidation of haemoglobin to methaemoglobin. T2 weighted images would give hypointense areas. Using 4 mm cuts we would expect to detect 80% of bleeds 3.2 mm in diameter. We have not detected subclinical bleeding in this group of patients.

Keywords: epidural haematoma; magnetic resonance imaging

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Breath interval variance in anaesthetized patients breathing spontaneously receiving remifentanil infusion i.v.

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We have studied breath interval as a measure of dynamic opioid effect during remifentanil infusion i.v. In a previous study of single doses of fentanyl and alfentanil i.v.,[1] breath interval appeared to vary more at peak drug effect.

Patients admitted for elective knee replacement surgery were studied. Anaesthesia was induced with propofol and maintained with 0.8% isoflurane and 67% nitrous oxide in oxygen through a laryngeal mask. Sciatic and three-in-one femoral blocks were performed with 0.375% bupivacaine. A Capnomac Ultima (Datex) measured carbon dioxide concentrations sampled at the laryngeal mask. Its analogue output was digitized at 100 Hz and logged to a PC. Analysis of the trace identified a point on the downstroke of the carbon dioxide waveform. Breath interval was the time between successive points. Baseline breath intervals were recorded in theatre and for 5 min after skin incision to identify any effect of surgery. Remifentanil 0.02 mg kg min^{-1} was then infused i.v. until the end of surgery, and breath interval recorded throughout. Statistical analysis was by Wilcoxon signed-ranks test.

Twenty-four patients were studied. Nerve blocks were inadequate in four, the computer failed once, one patient required assisted ventilation and one patient required the laryngeal mask to be changed to an endotracheal tube before nerve block. Data are presented for 17 patients. Patients were aged 61 (range 31–78) yr, weighed 74 (10) kg (mean (SD)), with height 171 (13) cm. Ten were male. The time taken to reach dynamic effect steady state, identified as the plateau of the breath interval curve, was 17.2 (4.7) min. The breath interval was 3.0 (0.8) s at baseline and 6.1 (2.1) s at steady state. The end-expired carbon dioxide concentration was 6.7 (0.8)% at baseline, rising to a peak of 7.9 (1)% during remifentanil infusion. The breath interval variance at baseline was 0.032 (0.013–0.059) s^2 (median (interquartile range)) and 0.240 (0.081–1.234) s^2 during the steady state plateau. The differences from baseline to plateau in breath interval (P=0.003), carbon dioxide concentration (P=0.005) and breath interval variance (P=0.003) were all significant.

Calculating time to dynamic steady state as five elimination half-lives gives a mean dynamic half-life of remifentanil of 3.4 min. This is similar to the context-sensitive dynamic half-time of 5.4 (1.8) min for remifentanil measured from minute volume, but less than the kinetic elimination half-time of 11.8 (5.1) min in the same volunteers.[2] There was a significant increase in breath interval variance during remifentanil infusion i.v.

Keywords: breath interval; variability

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Differential effects of propofol on *in vitro* release of interleukin 10 in response to lipopolysaccharide or concanavalin A

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In vitro and *in vivo* modulation of the release of some cytokines by propofol has been reported and may be particularly relevant in critically ill patients on intensive care units where such drugs are used for long periods by infusion. However, the effect on interleukin 10 (IL-10) has not been studied. We investigated the effect of propofol on lipopolysaccharide (LPS) or concanavalin A (Con A) stimulated IL-10 release.

Blood samples were obtained from 10 healthy volunteers. Whole blood was cultured for 24 h (LPS) or 48 h (Con A) in the presence of LPS 1 μg ml^{-1} or Con A 20 μg ml^{-1} or saline, plus propofol 0–50 μg ml^{-1} or Intralipid as a solvent control. Plasma IL-10 concentrations were measured using enzyme immunoassay. Data were analysed using Friedman analysis of variance with Wilcoxon signed rank *post hoc* testing.

IL-10 increased significantly in the presence of LPS or Con A ($P<0.0001$), although LPS-mediated IL-10 release was greater than with Con A ($P<0.0001$). In LPS-stimulated blood, IL-10 release was significantly increased in a dose-dependent manner in the presence of propofol ($P<0.001$). In blood stimulated with Con A, IL-10 was not altered by propofol. However, Con A- but not LPS-mediated IL-10 production by Intralipid treated blood was higher than that with saline ($P<0.05$).

Con A acts on T cell receptors such that IL-10 release is from T cells only. LPS acts on monocytes and neutrophils to produce other cytokines which in turn stimulate IL-10 release from several cell types. Our data show that propofol potentiates LPS-stimulated IL-10 but has no effect on T cell receptor mediated responses. The effect of Intralipid on T cell IL-10 confirms previous reports of effects on T cell proliferation. These data are interesting but highlight the importance of defining conditions for studies of *in vitro* immunomodulation by anaesthetics. The clinical relevance remains unclear.

Acknowledgement

We are grateful to the Intensive Care Society for financial support

Keywords: interleukin-10; propofol

Recovery profiles following daycase laparoscopic sterilization: a comparison of two anaesthetic techniques

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Total intravenous anaesthesia (TIVA) is associated with reductions in risk of postoperative nausea and vomiting and provides a rapid early recovery. It is generally more costly than an inhalational

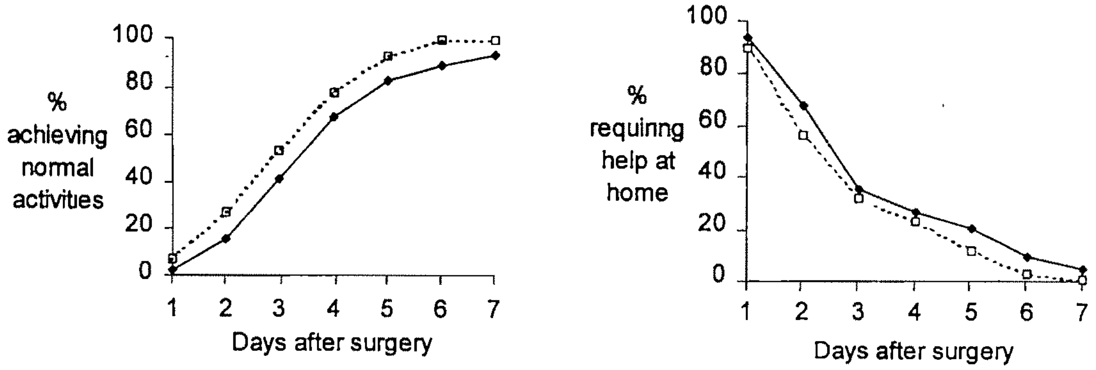

Fig 10 Functional recovery of patients during the 7 days after sterilization. Percentages of patients reporting in a structured interview that they had achieved their normal daily activities or required help at home Dashed lines and open squares represent patients who received total intravenous anaesthesia; continuous lines and filled diamonds represent patients in whom anaesthesia was maintained with isoflurane and nitrous oxide.

technique. Few data describe longer-term recovery from day surgery.

Ninety-nine females aged 35 (4.9) yr (mean (SD)), weighing 65 (10.7) kg who were undergoing laparoscopic sterilization by tubal ligation were allocated randomly to receive TIVA with propofol 6–10 mg Kg^{-1} and fentanyl 1.5 $\mu g\ Kg^{-1}$ or inhaled anaesthesia with propofol, fentanyl, nitrous oxide 66% and isoflurane 0.8% ET. A laryngeal mask airway was inserted and patients breathed spontaneously during surgery. All patients received diclofenac 100 mg PR and bupivaccine 0.5%, 10–20 ml. Recovery parameters were recorded. Patients were followed up with a daily structured telephone interview for 7 days.

Two patients were withdrawn from the study; one for a protocol violation and one with ectopic beats. Five patients were admitted to hospital; of these, two were in the inhaled group (one for drowsiness/nausea and one for pain control) and three in the TIVA group (two for surgical observation and one for pain control). Ninety-two patients completed follow-up for 24 h. Eighty-seven patients completed 7 day follow-up. There were no significant between-treatment differences in recovery parameters or patient outcomes over 1 week. Functional recovery from surgery was slow, with one-fifth of patients unable to complete normal daily activities by 4 days after surgery (Fig. 10).

Inhalational maintenance of anaesthesia is clinically satisfactory for laparoscopic tubal ligation performed as a day surgery procedure and does not importantly delay patient recovery or adversely affect postoperative outcome. Full recovery from this procedure may take up to 1 week.

Acknowledgement

P.J.V. was partly supported by Astra-Zeneca.

Keywords: propofol; isoflurane; day surgery

Absorpton of carbon dioxide after gynaecological laparoscopy

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As much as 180 ml of carbon dioxide can be left in the abdomen immediately after gynaecological laparoscopy;[1] this makes a significant contribution to pain the day after surgery How quickly is gas absorbed and for how long does it contribute to postoperative pain?

Patients undergoing daycase laparoscopic procedures were recruited at the preoperative assessment clinic. Surgery and anaesthesia proceeded as appropriate. It was hoped to take an erect X-ray of the diaphragm immediately before discharge and a further film the next day, by inviting patients back to hospital. However, not all patients recruited were fit for discharge before closure of the X-ray department (4.30 p.m.) and so these patients were instead invited to attend for X-rays 24 and 48 h after surgery. The volume of residual gas was estimated by measurement of bubble height and arc length as described previously,[1] by the same consultant radiologist. The minimum detectable volume was estimated to be 0.1 ml.

Telephone follow-up assessed pain attributable to the abdominal wound and residual gas (shoulder tip pain, high back pain), for the periods 0–24 h and 24–48 h after surgery, on a verbal incremental scale (0–10). Patients' suitability to attend for X-ray was also confirmed.

A total of 25 patients were recruited. Of these; three were not followed up because they could not be contacted by telephone, two were too ill to come in and three returned only 48 h postoperatively. This left 10 patients who had X-rays taken at 0 and 24 h after surgery and seven who had X-rays taken 24 and 48 h after surgery.

The results are shown in Fig. 11. The median total volume was 13.7 ml (range 4 5–76.2 ml) immediately after surgery, 1.4 ml (0–12.2 ml) after 24 h and 0.1 ml (0–1.5 ml) after 48 h. In all patients, the gas volume diminished with time. For the first 24 h after surgery, the median abdominal pain score was 4 (range 0–10) and the median gas-related pain score 5.5 (range 0–10). These had fallen to 3 (0–10) and 1.5 (0–6), respectively, by 48 h.

We conclude that virtually all gas is absorbed by 48 h after gynaecological laparoscopy, and that by this time it contributes little to postoperative pain.

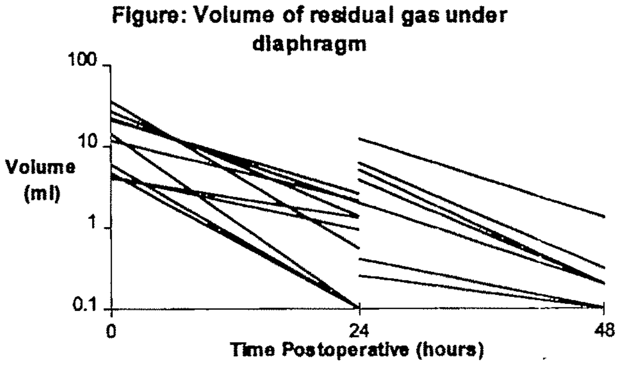

Fig 11 Volume of residual gas under diaphragm

Table 9 Numbers needed to treat for the prevention of PONV

Dose	*n*	Number needed to treat	
		Nausea	Vomiting
20 µg kg^{-1}	55	48.3 (NNTH 7.6 to NNTB 4.5)	17.6 (NNTH 10.1 to NNTB 4.0)
40 µg kg^{-1}	130	5.6 (NNTB 3.5–12.3)	5.5 (NNTB 3.5–10.9)
100 µg kg^{-1}	55	4.5 (NNTB 2.4–16.1)	3.9 (NNTB 2.3–10.1)
0.1 mg	260	7.4 (NNTB 4.0–20.5)	5.7 (NNTB 3.5–12.5)
1 mg	297	3.8 (NNTB 2.5–6.4)	3.3 (NNTB 2.35–5.2)
3 mg	273	4.3 (NNTB 2.9–7.2)	3.4 (NNTB 2.4–5.1)
4 mg	30	10.0 (NNTH 26.6 to NNTB 4.2)	10.0 (NNTH 139.9 to NNTB 4.8)

Acknowledgement

We thank Lancashire Ambulance NHS trust for patient transport.

Keywords: laparoscopy, carbon dioxide, absorption

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Systematic review and meta-analysis of studies of granisetron for the prevention of postoperative nausea and vomiting

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Tramèr and colleagues have reviewed the efficacy of ondansetron for the prevention of postoperative nausea and vomiting (PONV).[1] Their systematic review provides estimates of the number needed to treat for various doses of ondansetron when given to prevent PONV. Granisetron, rather than ondansetron, is provided for use in adults in our hospital. We therefore conducted a systematic review and meta-analysis of the available data on the use of granisetron for the prevention of early PONV (0–6 h after surgery) in adults.

MEDLINE was searched for studies of the efficacy of granisetron. The manufacturer also provided a list of relevant published studies. We identified 20 randomized controlled trials that compared granisetron with placebo for the prevention of PONV in adults following general anaesthesia. (A list of these is available from the authors.) Eight studies, including 1606 patients, contained relevant data. Data on the numbers of treated and control patients who did and did not suffer early emetic events were extracted from each paper. The data were pooled using a fixed-effects model.[2] The number needed to treat (benefit) (NNTB) was calculated for each dose of granisetron for which data were available.[3] Ninety-five per cent confidence limits were calculated in terms of NNTB and, where appropriate, number needed to treat (harm) (NNTH). The results are presented in Table 9.

The analysis of studies of variable-dose regimens (expressed in µg kg^{-1}) suggested a dose–response effect for the prevention of nausea. A similar effect was seen with variable-dose regimens for the prevention of vomiting. However, in both cases the confidence limits for the various doses overlapped. No clear dose–response effect was observed for studies of fixed doses of granisetron (expressed in mg) for the prevention of nausea or vomiting.

Acknowledgement

We are grateful to Dr Andrew Moore for his advice and for access to an Excel spreadsheet developed by the Oxford Pain Relief Unit to facilitate the calculation of numbers needed to treat

Keywords: granisetron; postoperative nausea and vomiting

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Recovery from sevoflurane anaesthesia when supplemented with remifentanil

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Previous studies have shown that the dose of propofol needed to maintain anaesthesia can be reduced significantly by supplementation with remifentanil, resulting in rapid early recovery.[1 2] The aim of the present study was to examine recovery from anaesthesia with sevoflurane when supplemented with remifentanil.

In 80 ASA I or II patients scheduled for elective surgery, anaesthesia was induced by inhalation of sevoflurane in nitrous oxide and oxygen. Patients were allocated randomly to one of four groups: group I received sevoflurane in concentrations necessary to maintain adequate anaesthesia, while patients in groups II, III and IV received 1.5, 1.0 and 0.5 MAC sevoflurane, respectively, and a remifentanil infusion. Patients in all groups received 66% nitrous oxide in oxygen. Remifentanil was administered in doses necessary to maintain adequate anaesthesia as judged by control of heart rate and arterial pressure, and absence of sweating, lachrymation and movement. The airway was maintained using a laryngeal mask airway (LMA) and ventilation was assisted to maintain normocarbia. Sevoflurane, nitrous oxide and remifentanil administration were stopped at the end of surgery and the times to eye opening, LMA removal and orientation were recorded by a blinded observer Psychomotor recovery and cognitive function was assessed by critical flicker fusion (CFF) tests at 15 min intervals and a mini-questionnaire assessing mental state was given 30 min after stopping anaesthesia. Postoperative analgesia was provided with tenoxicam, 0.15 µg/kg morphine and bupocaine infiltration. The results were analysed using Kruskal–Wallis tests.

The groups were comparable with regard to age, weight, height and duration of anaesthesia. Seven patients in group IV required a muscle relaxant to reduce chest wall rigidity. The dose of remifentanil used and times to eye opening, LMA removal and orientation are shown in Table 10. Significantly more patients were able to perform the CFF test at 15 min in group IV than in the other groups ($P<0.02$). There was no significant difference in mini-questionnaire test scores between groups at 30 min. The discharge time from the recovery ward was similar among the groups.

Table 10 Median (range) recovery characteristics for patients anaesthetized with sevoflurane (Sevo) alone or supplemented with remifentanil (Remi) *$P<0.001$ compared with group II, #$P<0.01$ compared with group I, $\$$$P<0.05$ compared with group I, †$P<0.001$ compared with group I, ‡$P<0.05$ compared with group II (Kruskal–Wallis test)

	Group I (control) Sevo only	Group II 1.5 MAC/Remi	Group III 1.0 MAC/Remi	Group IV (n = 19) 0.5 MAC/Remi
Time to eye opening (min)	10.3 (4.3–30.5)	12.8 (4.8–19.0)	11.0 (2.5–22.0)	6.5 (2.0–12)*#
Time to extubation (min)	11.5 (5.4–31.2)	13.8 (5.1–19.6)	11.3(3.0–23.0)	7.3(2.7–12.8)*#
Time to orientation (min)	12.1 (6.3–32.5)	14.9 (7.9–23.0)	12.1 (5.5–24.0)	8.3 (3.0–17)*$
Remifentanil μg kg^{-1}min^{-1}	0.0 (0.0)	0.21(0.06–0.32)†	0.25(0.15–0.4)†	0.34(0.19–0.49)†‡

In conclusion, the use of remifentanil was associated with a significantly faster early recovery when used for supplementation of low concentrations of sevoflurane, but was associated with chest wall rigidity in about a third of patients.

Keywords: sevoflurane; remifentanil; pharmacodynamics, recovery, interaction

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Antagonism of rocuronium block with neostigmine during sevoflurane, isoflurane or intravenous anaesthesia

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Previous studies have shown that the effects of rocuronium are potentiated during sevoflurane anaesthesia.[1] It has also been shown that some potent volatile anaesthetics can delay antagonism of neuromuscular block.[2] The present study was designed to assess the reversibility of rocuronium block during sevoflurane, isoflurane or intravenous anaesthesia.

One hundred and twenty ASA I or II patients undergoing elective surgery were enrolled into the study. Anaesthesia was induced with 1–2 μg kg^{-1} of fentanyl and 1–3 mg kg^{-1} of propofol and maintained with 66% nitrous oxide in oxygen and 1.5 MAC of sevoflurane or isoflurane (adjusted for age and nitrous oxide), or an infusion of propofol at 6–12 mg kg^{-1} h^{-1} (n=40 in each group). Neuromuscular block was monitored by stimulation of the ulnar nerve in a train-of-four (TOF) mode of stimulation and recording the force of contraction of the adductor pollicis muscle. Patients were given a bolus dose of rocuronium 0.6 mg kg^{-1}. Neostigmine 50 μg kg^{-1} (with glycopyrrolate 10 μg kg^{-1}) was given for antagonism of block at the end of surgery when T_1 (first response in the TOF) had recovered to approximately 25% of control. At the time of neostigmine administration, the patients were randomized to continue receiving sevoflurane (SC group), isoflurane (IC group) or propofol (PC group) in the same concentration/dosage, or to stopping sevoflurane (SS group) or isoflurane (IS group) or receiving a lower dose of propofol (PS group). Administration of nitrous oxide was continued until extubation. The time to attaining a TOF ratio of 0.8 was recorded, as was the number of patients in each group who had attained this endpoint within 15 min. The data were subjected to ANOVA and χ^2 tests.

The effect of neostigmine was apparent in <1 min in all groups. Those in the SC group took longest to attain a TOF ratio of 0.8, followed by the IC group (see Table 11). Four patients in the SC group and 1 in the IC group did not attain a TOF ratio of 0.8 within 30 min, this endpoint being attained only after sevoflurane was discontinued. In groups where the volatile agent administration was stopped during reversal, the times to attaining TOF ratio of 0.8 were not significantly different from the propofol groups. Significantly fewer patients in the SC group (9/20) had attained a TOF ratio of 0.8 within 15 min of neostigmine administration.

It is concluded that continued administration of sevoflurane during antagonism of a rocuronium block results in a prolongation of recovery from rocuronium. It is suggested that the volatile agent administration be discontinued at the time of antagonism of rocuronium block.

Keywords: neuromuscular relaxants, rocuronium; inhalational anaesthetics, sevoflurane. isoflurane; pharmacodynamics, interaction

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POSTERS

Does perioperative silent myocardial ischaemia predict long-term adverse outcome in surgical patients?

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Previous authors have investigated the relationship between silent myocardial ischaemia (SMI) and short-term postoperative complications after non-cardiac surgery.[1–3] There is little evidence, however, regarding its role in predicting long-term outcome.

Two hundred and fourteen patients undergoing non-cardiac surgery under general anaesthesia were monitored with continuous ambulatory ECG pre- and post-operatively. Other risk factors investigated were: age, hypertension, recent smoking,

Table 11 Recovery times, see text for abbreviations

	PC	PS	SC	SS	IC	IS
Mean (SD) time (min) to TOF ratio of 0.8	5.2 (2.8)	4.7 (1.5)	12 (5.5) (n=16)	6.8 (2.3)	9.0 (8.3) (n = 19)	5.5 (3.0)
No. attaining a TOF of 0.8 within 15 min	20/20	20/20	9/20	20/20	15/20	20/20

hypercholesterolaemia, diabetes mellitus, angina, previous myocardial infarction, admission for peripheral vascular surgery and medication. Patients were followed up while in hospital and for 12 months after surgery. The association between each factor and adverse outcome was determined using the χ^2 test with correction for small numbers.

There were 34 adverse events during the year after surgery. Twenty-four occurred within 6 months and the remaining 10 between 6 and 12 months. Five risk factors were associated with adverse outcome over both the first 6 months and for the whole year (Table 12). However, none of the factors examined was a predictor of long-term outcome (6–12 months).

These results are at variance with published data[2 3] and may reflect differences in the study populations and the incidence of confounding risk factors. We conclude that perioperative SMI does not aid the prediction of long-term cardiac complications

Acknowledgement

This study was supported by the Wellcome Trust and LMA International.

Keywords· myocardial ischaemia, outcome

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Fentanyl inhibits the delayed rectifier K+ current as part of its mechanism to improve recovery from ischaemic injury in isolated guinea-pig ventricular myocytes

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Ischaemic periods lasting for only several minutes can result in a reversible reduction in cardiac contractility known as cardiac ischaemic injury. Fentanyl ($C_{22}H_{28}N_2O$), a commonly used opioid analgesic, has been shown to improve recovery from cardiac stunning.[1] We sought to determine the underlying mechanism.

Single myocytes were isolated from guinea-pig ventricles and superfused with a balanced salt solution containing 2.5 mM Ca^{2+} (pH 7.4, 36°C). Cells were impaled with sharp microelectrodes (resistance approximately 50 MΩ) and stimulated at 1 Hz (pulse duration 2 ms, pulse amplitude 3 mV). Membrane potentials were recorded using an Axoclamp 2B amplifier in bridge mode under control conditions, during a 6 min application of fentanyl (100 nM, 300 nM, 500 nM and 1 μM) and during a 6 min washout.

In another series of experiments, the membrane potential was voltage-clamped at –40 mV (switched voltage-clamp) and the cells were stimulated at 0.1 Hz (pulse duration 500 ms; pulse amplitude 10 mV, then increasing by 10 mV with each stimulus until the amplitude reached 100 mV). Outward tail currents on repolarization largely represent delayed rectifier K^+ currents. These currents were recorded under control conditions, during a 6 min application of 1 μM fentanyl and during a 6 min washout. Paired Student's *t*-test was used to evaluate statistical significance.

Fentanyl (1 μM) caused a 16% increase in action potential duration measured as APD_{90} ($P<0.001$, $n=6$). This increase was reversible (APD_{90} returned to 103% of control after 6 min washout) and dose-dependent over the range 100 nm to 1 μM.

Fentanyl (1 μM) also caused a significant reduction in the amplitude of the outward tail currents after the pulse ($P<0.001$, $n=6$) when pulse amplitude was ⩾30 mV When pulse amplitude was 100 mV, 1 μM fentanyl reduced these currents to 55% of control, and a 6 min washout allowed recovery to 91% of control.

The observation that fentanyl inhibits outward tail currents following depolarization is consistent with inhibition of delayed rectifier K^+ currents. This inhibition would be expected to lead to the observed prolongation of APD_{90}.

Acknowledgements

This work was supported by the British Heart Foundation

Keywords: fentanyl; K^+ current

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Cerebroprotective effects of ketamine stereoisomers on rat forebrain metabolic activity after cerebral ischaemia

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Ketamine blocks *N*-methyl-D-aspartate (NMDA) receptors[1] and may thus be neuroprotective. It is optically active In the present report, we compared the effects of the enantiomers on tissue metabolism following global cerebral ischaemia.

Groups of >20 rat coronal corticostriatal slices (350 μm thick) were incubated in oxygenated artificial cerebrospinal fluid (CSF) at 34°C for 30 min, followed by a brief (10 min) ischaemic insult and further reincubation in oxygenated artificial CSF for 30 min. Ketamine or its enantiomers (100 μmol litre^{-1}) was/were present throughout the experiment. Slices were stained with 0.125% (w/v) 2,3,5-triphenyltetrazolium chloride (TTC), fixed in formalin and scanned using an 8-bit greyscale scanner (60 μm resolution).

Table 12 Association between perioperative SMI and other significant factors and adverse cardiac outcome in non-cardiac surgical patients Results shown as odds ratios (±95% CI)

Risk factor	Immediate (<6 months)	Long-term (6–12 months)	Overall (0–12 months)	Overall *P*
Perioperative SMI	4.44 (1.77–11.13)	1.01 (0.22–3.92)	2.81 (1.26–6.07)	0.01
Vascular surgery	17.09 (2.67–351.44)	1.12 (0.29–4.37)	4.34 (1.61–12.18)	0.002
History of angina	6.29 (2.21–17.62)	3.50 (0.48–18.36)	5.83 (2.15–14.83)	0.001
Calcium entry blockers	2.68 (1.03–6.93)	2.43 (0.51–9.69)	2.71 (1.09–6.31)	0.026
Smoker	4.93 (2.00–12.02)	–	2.30 (1.00–5.04)	0.036

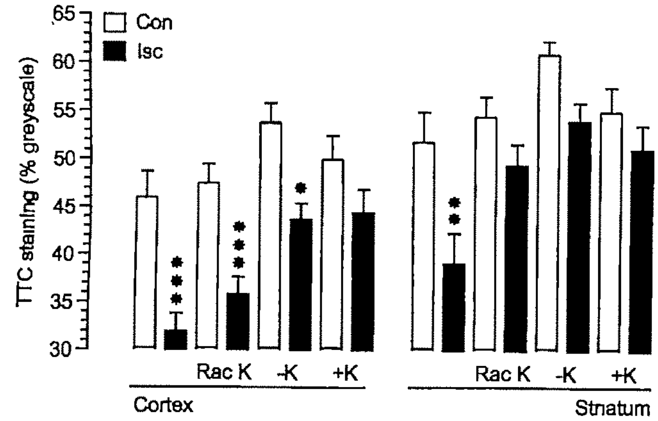

Fig 12 TTC staining of rat coronal corticostriatal slices after incubation in oxygenated artificial CSF with (Isc) or without (Con) a 10 min ischaemic insult in the presence of racemic ketamine (Rac K), (–)-ketamine (-K) or (+)-ketamine (+K).
* p<0.05
** p<0.01
***p<0.001

Striatal and cortical TTC staining was measured using Osiris software and expressed as a mean percentage greyscale.

In both striatum and cortex, 10 min of ischaemia reduced tissue metabolic activity by around 30% (striatum, $P<0.01$; cortex, $P<0.001$). Racemic ketamine (100 µmol litre^{-1}) prevented this loss of metabolic activity in the striatum but was ineffective in the cortex. (–)-Ketamine (100 µmol litre^{-1}) attenuated the loss of TTC staining in the striatum but had no effect in the cerebral cortex (Fig. 12), where ischaemia still produced a significant ($P<0.05$) reduction in staining. By contrast, (+)-ketamine (100 µmol litre^{-1}) was effective in both regions.

(+)-Ketamine is a better NMDA antagonist than the (–) isomer.[2] It is possible that the efficacy of (–)-ketamine in striatum but not cortex reflects a less severe insult in that region. Alternatively, different neurotoxic mechanisms may prevail in striatum and cortex. In cortex, for instance, excess activation of NMDA receptors by released glutamate may be the main mechanism while dopamine may contribute to ischaemic damage in striatum.

Acknowledgement

K.M. is the recipient of an Anaesthetic Research Society Vacation Scholarship.

Keywords: cerebral ischaemia; ketamine

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Magnesium sulphate and effects on cerebral haemodynamics in healthy volunteers

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Magnesium sulphate is being increasingly used in a variety of clinical conditions. It may have a role in the management of stroke[1] and closed head injury.[2] Its effects on cerebral autoregulation and carbon dioxide reactivity (CR_{CO_2}) are not well documented. We aimed to study the effect of a pharmacological dose of magnesium sulphate on middle cerebral artery (MCA) flow velocity, pulsatility index, cerebral autoregulation and CR_{CO_2} using transcranial Doppler ultrasonography.

Fifteen healthy volunteers were recruited. The left MCA was insonated and the probe was fixed with a headband The MCA flow velocity waveform was continuously recorded. A nose clip was applied and continuous end-tidal carbon dioxide ($ETCO_2$) monitoring was instituted via a mouthpiece. Arterial pressure was measured at 2 min intervals. Further monitoring consisted of continuous pulse oximetry and electrocardiography. MCA flow velocity, pulsatility index, cerebral autoregulation, CR_{CO_2} and serum Mg^{2+} concentrations were first assessed with the subject receiving no Mg^{2+} (baseline values). Cerebral autoregulation was assessed by performing a transient hyperaemic response test and calculating the strength of autoregulation.[3] CR_{CO_2} was assessed by measuring MCA flow velocity after induced changes in end-tidal carbon dioxide and calculated as per cent change in MCA flow velocity per kPa change in end-tidal carbon dioxide. These measurements were then repeated after a loading dose of 16 mmol Mg^{2+} over 15 min, followed by an infusion of magnesium at 2.7 mmol h^{-1} for 45 min. This regimen was based on the current IMAGES (MRC intravenous magnesium efficacy in stroke) trial. Blood samples were taken to measure serum Mg^{2+} concentrations before infusion and at steady state. The data were analysed using paired Student's *t*-tests.

Our results (Table 13) show that after administration of i.v magnesium sulphate, using the described regimen, there are no significant changes in MCA flow velocity, pulsatility index, cerebral autoregulation or CR_{CO_2} in healthy volunteers

Acknowledgement

This study was funded in part by the Department of Neurosurgery, University Hospital, Nottingham.

Keywords: magnesium sulphate; cerebrovascular circulation

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Table 13 Effects of magnesium on cerebral haemodynamics Mean (SD) *$P<0.001$

	Pre-magnesium	Steady-state magnesium
MCA flow velocity (cm s^{-1})	62.61 (12.82)	61.19 (13.29)
Pulsatility index	0.77 (0.19)	0.82 (0.31)
Strength of autoregulation	1.05 (0.14)	1.06 (0.14)
Carbon dioxide reactivity	37.92 (8.72)	37.27 (8.57)
Serum Mg^{2+} concentration (mmol litre^{-1})	0.78 (0.06)	1.57 (0.12)*

Does intraoperative surgical stimulation influence psychomotor recovery from anaesthesia?

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Much previous research into recovery of psychomotor function after anaesthesia for day-case surgery has focused on comparing different drugs or anaesthetic techniques. Very little consideration has been given to whether intraoperative surgical stimulation resulting from differing surgical procedures influences psychomotor recovery after anaesthesia.

The aim of the present study was to evaluate the influence of surgical stimulation on psychomotor recovery from anaesthesia using two methods of assessing psychomotor performance and a standardized anaesthetic technique.

The local ethics committee approved the project. We studied 50 healthy (ASA 1 or 2) patients of both sexes aged between 18 and 65 yr undergoing minor arthroscopic procedures on the knee or extraction of wisdom teeth as day cases. After obtaining written, informed consent, patients performed two tests of psychomotor ability before undergoing the type of surgery they had been scheduled for. The p-deletion test is a letter-cancellation task described by Dixon and Thornton.[1] The ADTRACK 2 is a one-dimensional pursuit tracking task with joystick control[2] which has been previously used to test psychomotor recovery from anaesthesia.[3] In both groups anaesthesia was induced using propofol. In the arthroscopy group, a laryngeal mask airway was inserted. Anaesthesia was maintained in all patients with 2% isoflurane in nitrous oxide (66%) and oxygen using a circle breathing system. In the wisdom teeth extraction group, tracheal intubation with a nasotracheal tube was facilitated by atracurium 0.5 mg kg^{-1} and the patients' lungs were ventilated.

Baseline measurements were made of blood glucose, pulse, arterial pressure, end-tidal carbon dioxide concentration and arterial oxygen saturation before induction of anaesthesia and then at 60 s intervals Blood glucose was measured at 180 s intervals. At the end of surgery all patients received 10 ml of plain 0 5% bupivacaine local infiltration. The time to eye opening was recorded by the recovery nurse. At 30 and 90 min, the psychomotor tests were repeated and a pain score and vomiting score were recorded.

The ages, weights, heights, duration of anaesthesia and preoperative psychomotor scores in the two groups were comparable. The increase in blood glucose during surgery was significantly greater in the dental surgery group (P=0.02) as was the increase in mean arterial pressure ($P<0.001$) and heart rate (P = 0.03). There was no difference between groups in intraoperative heart rate, end tidal carbon dioxide, arterial oxygen saturation, time to eye opening, pain scores, vomiting scores or postoperative psychomotor tests.

Keywords: anaesthesia, recovery

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Effect of halothane and isoflurane on left ventricular systolic function in isolated senescent rat hearts

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Studies on humans and animals *in vivo* have suggested that the cardiac depressant effect of volatile anaesthetic agents is greater in old subjects than in young ones;[1] studies on elderly rat hearts *in vitro* have demonstrated impaired diastolic function with prolonged isovolumetric relaxation period and increased myocardial stiffness,[2] but the effect of ageing on ventricular systolic function is less clear Since halogenated inhalational anaesthetics depress cardiac function mainly by alterations in intracellular Ca^{2+} regulation, and since impaired Ca^{2+} uptake by sarcoplasmic reticulum has been demonstrated in senescent rat heart,[3] we examined the effect of halothane and isoflurane on systolic function in isolated elderly rat hearts. Two groups of female Wistar rats were studied: young adults (3–5 months; 220–270 g) and aged adults (24–26 months; 240–360 g). Hearts were removed and perfused in Langendorff mode at a perfusion pressure of 80 mm Hg; systolic function was assessed by digitized pressure monitoring from an intraventricular latex balloon and offline differentiation ($+\mathrm{d}P/\mathrm{d}t_{\max}$). After baseline measurements, halothane or isoflurane was introduced at 1 or 2 MAC (published values for each age group) and measurements were repeated. Results were analysed by *t*-test and ANOVA for repeated measurements.

Wet weights of hearts were similar (young adult: 1.40±0.10 g; old: 1.45±0 10 g). After 20 min stabilization, baseline measurements of $+\mathrm{d}P/\mathrm{d}t_{\max}$ were similar in each group (young adult: 2516±234 mm Hg s^{-1}; old: 2550±109 mm Hg s^{-1}) but developed pressure (peak systolic pressure – end-diastolic pressure) was significantly less in the old hearts (70.5±2.5 mm Hg) than in young adult hearts (83.4±3.8 mm Hg; $P<0.05$). Despite this, there was no difference between old and young adult hearts in either $+\mathrm{d}P/\mathrm{d}t_{\max}$ (Fig. 13) or developed pressure (data not shown) with either anaesthetic agent or MAC value. Both agents decreased the developed pressure and $+\mathrm{d}P/\mathrm{d}t_{\max}$ These results suggest that, although the ageing process may affect left ventricular systolic function, the susceptibility of the myocardium to clinically relevant concentrations of halogenated volatile anaesthetic agents is unchanged, at least until the point of senescence where developed pressure is less than in young adult hearts but $+\mathrm{d}P/\mathrm{d}t_{\max}$ is preserved.

Keywords: ageing, halothane, isoflurane, systolic function

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Liver transplantation and blood loss: a 10 yr analysis

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Our aim was to compare two large groups of liver transplant data, assessing whether there has been an improvement in technique over time using intra-operative blood loss as the primary endpoint. Also, we wished to examine this large database to assess patient factors that would improve our ability to predict which patients are at risk of increased blood loss.

Details of patients undergoing liver transplantation at St James's

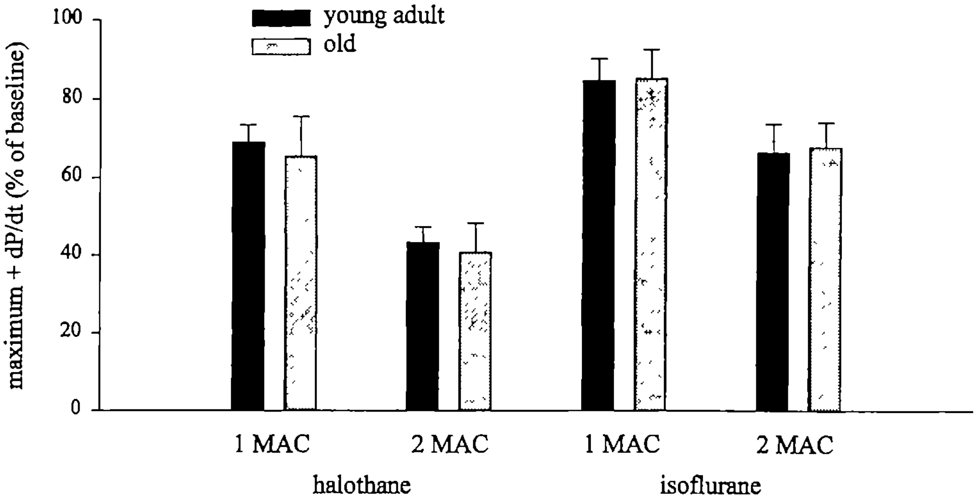

Fig 13 Maximum positive dP/dt in isolated old and young adult rat hearts Means±SE; n=6 or 7.

Hospital, Leeds were recorded in two databases, one for 1989–1995 (n=257) and one for 1996–2000 (n=409) We made direct comparisons between the two groups to assess any change over time. We also performed univariate and multivariate regression analysis, using blood loss as the dependent variable, to assess any correlation between patient factors and intra-operative blood loss.

The 'old' database has fewer numbers, as more patients were lost to audit in the earlier years. These deficiencies have been corrected in later years, resulting in a more complete 'new' database This has resulted in the 'old' data not performing well under statistical analysis, producing figures that could not account for the variability of the model. The 'new' data produced better results, with only six variables independently associated with intra-operative blood loss (P<0 0001) These were: patient age (P=0 07), presence of ascites (P=0 01), serum bilirubin (P=. 02), the historical placement of the transplant within the database (P=0 05), serum Na^+ concentration (P=0.04) and previous upper abdominal surgery (P=0.06). The variability explained by the model was calculated as 24%(r^2=0.24). Direct summary and comparison of the two sets of data demonstrated that intra-operative blood loss was lower in the new dataset than in the old one: 11.8 (95% CI 10.2–13.4) units of blood were used in the old dataset and 7.28 (6.6–7.9) units of blood in the new one (P<0.0001); the corresponding amounts of fresh frozen plasma used were 18.8 (17.4–20.1) and 15.3 (14.7–16.0) units, respectively (P<0.0001; Wilcoxon). Platelet and cryoprecipitate use were unchanged.

A general improvement in skills and technique is likely to explain the reduction in blood product use over time. Predicting blood loss from preoperative factors proved more difficult. Factors independently predictive of blood loss were similar to those previously described[1] and do not add to what we already consider risk factors for perioperative blood loss. Much of the variability was not explained by the model, and could have been due to independent factors such as intraoperative biochemical changes.[2]

Keywords: liver transplantation; blood loss; predictive modelling

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British Journal of Anaesthesia **85** (4): 656–70 (2000)

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Hyperbaric oxygen therapy

Editor,—Hawkins and colleagues'[1] review of 31 cases of severe carbon monoxide poisoning treated with hyperbaric oxygen therapy was interesting and highlights the high mortality (16.1%) and serious nature of this condition. However, their use of a historical control group treated with 'normobaric oxygen' from another study by Krantz and colleagues[2] with a mortality of 30% and a worse outcome may erroneously suggest that hyperbaric oxygen therapy has a marked benefit over normobaric oxygen in the severely poisoned patient. In Krantz's study though patient characteristics were similar, it was a retrospective review of cases over a 15-yr period between 1969 and 1983. Also the 'normobaric oxygen' treatment regimen was not standardized and in some cases limited to 1 h of 100% oxygen, unlike more modern prolonged (6 h) administration of high concentrations of oxygen Furthermore, as the authors point out, the use of hypothermia in some of the controls may have been detrimental to outcome. Variations in the quality of intensive care over the last 21 yr and the lack of a formal normobaric oxygen protocol may have led to the higher mortality rates and worse outcome in the control study.

Hyperbaric oxygen therapy for carbon monoxide poisoning remains unproven. Early trials suggesting benefit, were neither randomized nor controlled. To date there have been six prospective randomized trials, with some degree of blinding, comparing hyperbaric oxygen to normobaric oxygen. Two (n=91 patients) have shown some improvement in reducing the time to recovery[3] and reducing the incidence of delayed neuropsychological sequelae.[4] However, the other four trials[5–7] (n=1170 patients) showed no benefit from hyperbaric oxygen. In the most recent trial by Scheinkestel and colleagues[8] of 191 patients in which 73% were severely poisoned, there was no significant difference in mortality (3.4% compared to 3%) and there was no significant difference between the two groups for persistent neurological sequelae. However, there was a significant increase in the incidence of delayed neurological sequelae in the group treated with hyperbaric oxygen. The authors concluded that hyperbaric oxygen did not benefit and may have worsened the outcome.

Hyperbaric treatment is not without complications, the majority being minor cases of barotrauma and claustrophobic reactions. However, there is the risk of pulmonary oxygen toxicity, an incidence of oxygen-induced convulsions, and the potential for a chamber fire, which has led to deaths of both patients and attendants Severely poisoned patients are critically ill and may have a secondary acute lung injury from aspiration while they were unconscious; high doses of oxygen may worsen this injury. Finally these patients may be at increased risk from the transfer process alone especially if they have cerebral oedema and raised intracranial pressure.

A recent editorial in the *British Medical Journal*[9] concluded that though both normobaric and hyperbaric oxygen were accepted treatments for carbon monoxide poisoning, it remained unclear whether hyperbaric oxygen offered a substantial advantage. In the severely poisoned patient, the clinician must make a balanced judgement on the risks and benefits of transferring their patient for hyperbaric therapy, for which there seems to be increasing evidence suggesting little or no benefit over treatment with normobaric oxygen.

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9 Weaver L. Hyperbaric oxygen in carbon monoxide poisoning: conflicting evidence that it works. *Br Med J* 1999; **319**: 1083–4

Editor,—Hawkins and colleagues[1] reported a series of 31 cases of severe carbon monoxide poisoning requiring mechanical ventilation, who were treated with hyperbaric oxygen therapy. They compared outcomes with a historical control group of 79 similar patients treated with normobaric 100% oxygen[2] and conclude that hyperbaric oxygen 'appeared to reduce the risk of serious neurological deficit and the need for prolonged care'.

While they are to be congratulated on an excellent audit of their own unit's performance, as well as for producing an improvement in outcome compared to a period 31–17 yr ago (1969–1983),[2] it is not justified to infer that this improvement is due to hyperbaric oxygen therapy. Furthermore, it is inappropriate to lend validity to the comparison by the application of statistical tests of significance, when it is not reasonable to assume that the two groups are from similar populations. The data are uncontrolled, retrospective, from different countries, by different authors in different eras, with very different normobaric treatment strategies. In Krantz's series,[2] 79% received glucocorticoids, 61% were treated with additional hypothermia (30–34°C), all had barbiturate infusions and 78% were hypotensive. Before the institution of mechanical ventilation, 100% oxygen was administered for a minimum of 1 h, but the inspired oxygen concentration was unspecified thereafter. Furthermore, the types of carbon monoxide exposure were very dissimilar, 12.9% *vs* 87% from exposure to household gas installations and 54.8% *vs* 5% due to poisoning from car exhausts, comparing Hawkins[1] and Krantz[2] respectively. The relative duration and concentration of exposure, time to resuscitation, time to application, duration and method of 100% oxygen therapy are not reported, all of which can reasonably be expected to affect outcome without prospective randomization.

In contrast to Hawkins and colleagues' comparison of disparate

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data, a recent randomized, prospective, double blind study, including sham treatments, has shown that hyperbaric oxygen therapy results in a significantly worse outcome in both mild and severe poisoning, compared with three days of optimal normobaric oxygen therapy.[3] Three randomized prospective trials[3–5] involving 1395 patients have now shown no benefit from hyperbaric oxygen therapy, compared with two studies[6 7] totalling 91 patients, demonstrating benefits for mild poisoning only. All these studies can be criticized, but as there are significant risks from hyperbaric oxygen therapy and transportation,[3 8] the current evidence base indicates that hyperbaric oxygen should not be used for the treatment of acute carbon monoxide poisoning. The indications for hyperbaric oxygen therapy[9] so widely promulgated should be revised and resources should be concentrated on prevention, rapid resuscitation and early, prolonged application of 100% normobaric oxygen. NHS resources may well be being wasted on an outdated, dangerous therapy.

The literature is littered with interesting anecdotes on the treatment of carbon monoxide poisoning, with hyperbaric oxygen, often by authors with a commercial interest. At best, the report by Hawkins and colleagues[1] adds little to the evidence base and, at worse, it is misleading.

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1 Hawkins M, Harrison J, Charters P. Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy *Br J Anaesth* 2000; **84**: 584–6
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Editor,—Thank you for the opportunity to reply to this correspondence. The impetus to publish audit of the work of a current UK hyperbaric unit where the medical staff are ICU trained anaesthetists was the sudden and dramatic nature of deaths from cerebral oedema. It occurred at 24–48 h when we considered the risk should be decreasing. Previously published work was unhelpful and there was no comparative trial of severely poisoned patients, hence the reference to the audit of Krantz and colleagues.[1] Obviously both authors and reviewers were aware of the limitation or irrelevance of statistical comparison but the outcry if there was no formal comparison would probably have been greater. There have been many trials of hyperbaric oxygen treatments for carbon monoxide poisoning, none of which appear to have been free from criticism. The main problems continue to be absence of reliable markers for disease severity or likelihood of 'delayed neurological syndrome', difficulty in eliminating the potential for placebo effects and variability in treatments between centres. When reports put 'severe' and 'moderate' poisoning together it is usually impossible to make inferences without resorting to unjustifiable assumptions. The limited referencing and discussion in our paper was forced on the authors by an early editorial decision to offer a 'Short communication'.

Our clinical practice is to treat acutely carbon monoxide-poisoned patients within 6 h of their rescue. Anticipated treatments without this 'treatment window' would not normally be accepted. (We would regard the few treated beyond this time in our series as administrative failures.) The reason we did not refer to the trial by Scheinkestel and colleagues[2] was firstly that it did not describe only artificially ventilated patients. In a comparison where the 'hyperbaric oxygen protocol was designed to produce maximal potential advantage for hyperbaric oxygen therapy', we are at a loss to understand what this means. Hardly any of their ventilated and hyperbaric oxygen-treated patients appear to have been treated within the generally accepted 'treatment window'. As far as we are aware, they are the first group to suggest that hyperbaric oxygen treatment is worse than normobaric oxygen alone. For many years, there has been a dispute as to whether hyperbaric oxygen is more effective than normobaric oxygen in lesser degrees of poisoning. The neuropsychological performance outcome measures on which their claims are based have been suggested to be extremely dubious on almost every count that might be considered relevant by neuropsychiatrists.[3] In addition, their results appear to include the very strange paradox that the less severely poisoned patients were significantly worse with normobaric oxygen than hyperbaric oxygen.[4]

Why Scheinkestel's group showed a worse outcome with normobaric oxygen than hyperbaric oxygen could simply have been that they gave an equivalent total dose of oxygen and theirs was the first trial to use such a protocol. However, there also remains the obvious question as to whether their groups were, in fact, comparable. Despite the small number of ventilated patients they state that any differences were allowed for by multiple logistic regression. They concede the possibility of type 1 errors on the grounds of multiple comparisons but with smaller subgroupings the risk of type 2 errors are increased. Their contention that 'all the differences were consistent and suggested a more detrimental outcome in the hyperbaric oxygen group' is hardly consistent with the paradox referred to above. The circumstances for carbon monoxide poisoning in Australia are very different from Europe because they reported mainly suicide attempts with very few patients over 40 yr The only reasonably consistent surrogate marker for severity in carbon monoxide poisoning is metabolic acidosis. This related to good/poor outcome in both our audit and that of Krantz. Acidosis is hardly mentioned in Scheinkestel's paper and the overall incidence was only 12.6%. On the other hand, Scheinkestel at least raised awareness of the comparable oxygen dose delivery and this may prove to be important when supported by other studies.

Hyperbaric oxygen cannot necessarily be assumed to be just about displacement of carbon monoxide by oxygen. Evidence for a postischaemic reperfusion injury is increasing as is information about the relevance of hyperbaric conditions in treatments[5–7] Even the notion that oxygen dose is all that matters has to be seen in context. We were very aware of gas exchange problems during the period of our audit. Smoke inhalation, aspiration while unconscious and other pulmonary complications are common in carbon monoxide poisoned patients requiring ventilation Normal oxygen delivery and carbon monoxide elimination cannot be assumed and the implications, although inadequately investigated, may be far-reaching especially for patients only treated with normobaric oxygen.

The senior authors in our paper have both been involved in moves by the British Hyperbaric Association to set up a multicentre trial of hyperbaric oxygen in severe carbon monoxide poisoning. This must be in centres capable of full ICU support and the hyperbaric oxygen treatments should be given as early as possible after exposure. Obviously transfer to and treatment in a hyperbaric centre does involve some risk but this was not an important problem in any of our cases. Prevention of carbon monoxide poisoning is clearly the ideal and much has already happened to this end. For seriously poisoned patients however, any potential to reduce the high mortality and/or morbidity must receive due consideration.

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Acknowledgement

J. Harrison is Medical Director of the North West Emergency Recompression Unit.

Rectal paracetamol has a significant morphine-sparing effect after hysterectomy

Editor,—We read with interest the article by Cobby and colleagues[1] who investigated the analgesic efficacy of rectal paracetamol for postoperative analgesia after abdominal hysterectomy. In their study, a dose of rectal paracetamol 1.3 g which was administered at the end of surgery, and repeated 8 and 16 h thereafter, resulted in a significant morphine-sparing effect during the first 24 h after surgery. Even a single dose of paracetamol 1.3 g (~20 mg kg^{-1} in adults) given at the end of surgery was found to be effective, since morphine consumption in the paracetamol group decreased significantly in the early postoperative period.

These findings are contrary to our results obtained from a similar patient population.[2] We were unable to detect any significant differences in pain intensity and the use of self-administered morphine at any time during the first 24 h after surgery between women who received a single dose of 20 mg kg^{-1} and those who were given paracetamol 40 mg kg^{-1} rectally. We also failed to establish a relationship between plasma concentrations and analgesic efficacy of paracetamol.

Analgesic effects have been assumed to occur at plasma concentrations known to produce antipyresis (10–20 mg $litre^{-1}$), although analgesic paracetamol plasma concentrations have never been defined. The authors cited the only clinical investigation that provides some evidence of a relationship between plasma concentrations and analgesic efficacy.[3] A dose of oral paracetamol 40 mg kg^{-1} was used as the sole analgesic in children undergoing tonsillectomy; plasma concentrations of 25 mg $litre^{-1}$ gave satisfactory analgesia in 60% of children. However, the situation may be different if paracetamol is given in conjunction with opioids for postoperative analgesia in adults.

In our patients, the administration of paracetamol 20 mg kg^{-1} resulted in subtherapeutic plasma levels (<10 mg $litre^{-1}$), a dose of 40 mg kg^{-1} produced antipyretic plasma concentrations, but was not associated with better analgesia or decreased opioid requirements. Possible reasons for these findings are that (a) analgesic plasma concentrations are higher than those associated with antipyresis, (b) the methodology of measuring opioid intake may not be sensitive enough to detect small differences resulting from the weak analgesic effects of paracetamol and (c) a ceiling effect may occur at low paracetamol plasma concentrations.

We agree with Cobby and colleagues, that paracetamol may be a useful adjunct to PCA morphine, but its exact role for postoperative analgesia in adults has yet to be established. This applies in particular to the dose and the dosing intervals that are required to attain and sustain effective analgesic plasma concentrations.

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1 Cobby TF, Crighton IM, Kyriakidis K, Hobbs GJ. Rectal paracetamol has a significant morphine-sparing effect after hysterectomy. *Br J Anaesth* 1999; **83**: 253–6
2 Beck DH, Schenk MF, Hagemann K, Doepfmer U, Kox WJ. Pharmacokinetics and analgesic efficacy of larger-dose rectal acetaminophen in adults: a randomized double-blinded study. *Anesth Analg* 2000; **90**: 431–6
3 Anderson B, Kanagasundarum S, Woollard G. Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. *Anaesth Intensive Care* 1996; **24**: 669–73

Editor,—We thank Dr Beck and colleagues for their interest in our paper.[1] We have also read their paper[2] with interest. This demonstrated no significant differences in pain intensity after hysterectomy between patients receiving two different doses of rectal paracetamol (20 mg kg^{-1} and 40 mg kg^{-1}) and no difference in the use of self-administered morphine at any time during the first 24 h after surgery. They concluded that there was no relationship between plasma paracetamol concentrations and analgesic efficacy. We do not think our findings can easily be compared. We would make several points.

First, our patient populations were not similar. All of our patients underwent abdominal hysterectomy. Beck's patients underwent either abdominal or vaginal hysterectomy, with the latter constituting the majority of patients in each group (about

70%). In our clinical experience, abdominal hysterectomy may be a more painful operation and therefore our model may have been a more sensitive clinical assay of analgesic efficacy. Dr Beck does acknowledge this possibility in their paper.

Second, the use of self-administered morphine doses to assess analgesic efficacy may be contentious, but differences can be demonstrated. Differences in pain scores are perhaps less likely where patients are allowed to titrate their analgesic dose to effect and therefore we would place less significance on pain scores alone as outcome measures in this type of study. However, differences have been demonstrated.[3]

Third, we used repeat dosing of paracetamol. This is likely to have led to a greater AUC for plasma paracetamol concentrations during the 24 h study period than Dr Beck's single (lower) dose method and therefore possibly greater efficacy over the 24 h study period, particularly when assessing morphine consumption data.

Fourth, we compared rectal paracetamol to placebo and are therefore confident that our research model and conclusions were robust. There are other data to support the opioid-sparing effect of paracetamol.[4 5] Our placebo-controlled study is quite different to a design comparing the efficacy of two doses of paracetamol (that may require a larger sample size to avoid type 2 errors). Without a placebo group, it is difficult to establish if the lower dose of rectal paracetamol had any analgesic efficacy in Beck's study. Therefore, the conclusion that the lower dose was subtherapeutic cannot be made unless this term refers to the concentrations being less than those required for antipyresis (10–20 mg litre^{-1}) and not analgesia. Dr Beck's study does suggest that there was no clinically important, dose-related change in efficacy between the two doses (20 mg kg^{-1} and 40 mg kg^{-1}).

The results of our studies taken together may actually support our suggestion that the analgesic efficacy of paracetamol may have a ceiling (NSAIDs such as diclofenac are also recognized to have a ceiling effect) when used with self-administered morphine and that this ceiling is at low rather than high concentrations. This has been considered by Beck in his letter. However, the true analgesic concentration-effect relationship remains contentious[6] and has not been fully established. Even in the absence of these data, we considered rectal paracetamol to have a useful role in managing postoperative pain, as do others.[3] Beck's kinetic data (plasma concentrations of paracetamol appear to plateau for more than 8 h after a single dose; supported by our unpublished data) suggest that rectal paracetamol may best be delivered with a twice daily dosing schedule, perhaps in higher doses.

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1 Cobby TF, Crighton IM, Kyriakides K, Hobbs GJ. Rectal paracetamol has a significant morphine-sparing effect after hysterectomy. *Br J Anaesth* 1999, **83**: 253–6

2 Beck DH, Schenk MF, Hagemann K, Doepfmer U, Kox WJ. Pharmacokinetics and analgesic efficacy of larger-dose rectal acetaminophen in adults: a randomized double-blinded study. *Anesth Analg* 2000; **90**: 431–6

3 Schug SA, Sidebotham DA, McGuinnety M, Thomas J, Fox L. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. *Anesth Anal* 1998; **87**: 368–72

4 Regular paracetamol dosing reduces narcotic requirements in treating postoperative orthopaedic pain. *Austr J Hosp Pharm* 1995; **25**: 13–17

5 Delbos A, Boccard E. The morphine-sparing effect of propacetamol in orthopedic postoperative pain. *J Pain Symptom Manage* 1995; **10**: 279–86

6 Piguet V, Desmeules J, Dayer P. Lack of acetaminophen ceiling effect on R-III nociceptive flexion reflex. *Eur J Clin Pharmacol* 1998, **53**. 321–4

Sedation of children by non-anaesthetists

Editor,—We would like to offer some words of caution before UK anaesthetists advocate nurse administration of sedation to children undergoing magnetic resonance imaging (MRI) in order to cope with the increased demands for this service, as recently discussed in your journal.[1 2] Sedation of children within MR scanners poses a unique set of problems due to the remote location of many units; the duration and depth of 'sedation' required which means that verbal contact is not maintained; the difficulty of observing and monitoring the children within the scanner, and the need for rapid recovery to enable this to be performed as a day-case procedure.

There are at least 46 MRI units in the UK and Ireland performing anaesthesia for patients undergoing imaging.[3] As many of these units are in a remote area within the hospital complex it cannot be assumed that an anaesthetist is readily available to help manage critical events. The MRI unit in the papers from Great Ormond Street Hospital and Manchester Children's Hospital describing nurse administered sedation in the UK may have been close to a theatre complex with an arrangement for anaesthetist assistance if required.[4 5] It is interesting to note that the nurse sedationists in the paper by Malviya and colleagues were supervised by a radiologist.[2] It has been shown that hypoxaemia, respiratory depression or airway obstruction may occur during oral sedation in children, even when chloral hydrate is administered within the recommended dose range as the sole sedative agent.[6] It is unlikely that many UK radiologists will be willing to accept clinical responsibility for children with such risks involved, as this would require supervision of airway management skills that they may not possess. It is also unlikely that anaesthetists will be willing to accept clinical responsibility for a remote area, even if they have designed and written the sedation protocols and trained the nurse sedationists. If the nursing profession decides it wishes to extend its role in this area, it must be prepared to accept responsibility for any potential insults caused to patients by their interventions, even if these are within the limits of local protocols written by doctors. We doubt if the nursing profession in the UK is willing at this stage to do so.

Our second area of concern relates to the assumption that the use of nurse sedationists in MRI units will save money compared to anaesthetist-delivered general anaesthesia.[2] This may not be the case. The prolonged onset and recovery times of orally administered sedation require ward facilities not employed in many MRI units in the UK currently using anaesthetic services only.[3] This involves capital and running costs with additional nursing staff and transport facilities that must be taken into consideration. In addition, there are a small number of children who require overnight admission due to the effects of sedation.[2 4 5] In our unit, out of 750 elective day-case paediatric MR scans under general anaesthesia performed in the past 3 yr there has not been a case in which an overnight stay has been required. Malviya and colleagues argued that general anaesthesia resulted in a longer duration of recovery than oral sedation, as demonstrated in their study.[2] This is a surprising result and would certainly not be expected in the hands of most UK paediatric anaesthetists using appropriate general anaesthetic techniques and drugs.

Malviya and colleagues, Sury and Keengwe described failed nurse sedation rates for MR scanning of 9.6%, 5% and 7% respectively requiring the procedure to be abandoned with subsequent imaging under general anaesthesia.[2 4 5] It is unclear whether Keengwe took this cost into consideration when calculating the reduced cost of a MRI scan under sedation as compared to general anaesthesia[5] We would suggest that the additional salary involved in employing a consultant anaesthetist to administer general anaesthesia as opposed to a nurse's salary to administer sedation would not be significant when all these issues are taken into account. It is to be expected that the overheads of anaesthetic equipment and monitoring will be applicable in all units providing sedation and/or anaesthesia, as it is accepted that general anaesthesia is required for certain children in whom sedation is contraindicated.[2]

Our final concern relates to the government's drive for a quality agenda in the National Health Service. The need for the administration of sedation for children undergoing MRI by non-anaesthetists has arisen due to a shortage of anaesthetic resources. In at least 25 units in the UK and Ireland, sedation is being administered to patients undergoing MRI by radiologists or paediatricians.[3] Although UK anaesthetists cannot instruct these medical specialties how to manage their patients, we can publish guidelines for the management of patients undergoing MRI under sedation. A recommendation for the Association of Anaesthetists to produce such a document has been made.[3] We would argue that some form of respiratory monitoring is recommended during the use of sedative techniques within MRI units in which verbal contact is not maintained because pulse oximetry only detects critical hypoventilation or airway obstruction some time after the event occurs. Observation of an expired carbon dioxide trace would give the earliest detection of such events.

We doubt whether it could be argued that a structured nurse sedation programme improves the quality of a MRI service, except with regards to waiting times. If anything, with the incidence of abandoned procedures as stated, and the poorer quality of images obtained,[2] the overall quality of the service appears to be significantly inferior. Are we, as the anaesthetic consultant body in the UK, prepared to advocate an inferior service to patients due to a lack of resources within our own departments? Surely our position should be one of campaigning for more consultant anaesthetists to provide the service required. If the quality agenda is to be pursued, then let us not compromise ourselves by advocating an inferior service that may not, in fact, have any cost benefits.

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1 Hatch DJ, Sury MRJ. Sedation of children by non-anaesthetists. *Br J Anaesth* 2000; **84**: 713–14
2 Malviya S, Voepel-Lewis T, Eldevick OP, Rockwell DT, Wong JH, Tait AR. Sedation and general anaesthesia in children undergoing MRI and CT: adverse events and outcomes. *Br J Anaesth* 2000, **84**· 743–8
3 McBrien ME, Winder J, Smyth L. Anaesthesia for magnetic resonance imaging—a survey of current practice in the UK and Ireland *Anaesthesia* 2000; **55**: 737–43
4 Sury MRJ, Hatch DJ, Deeley T, Dicks-Mireaux C, Chong WK Development of a nurse-led sedation service for paediatric magnetic resonance imaging. *Lancet* 1999; **353**: 1667–71
5 Keengwe IN, Hegde S, Dearlove O, Wilson B, Yates RW, Sharples A. Structured sedation programme for magnetic resonance imaging examination in children. *Anaesthesia* 1999; **54**: 1069–72
6 Malviya S, Voepel-Lewis T, Tait AR. Adverse events and risk factors associated with the sedation of children by nonanaesthesiologists. *Anesth Analg* 1997; **85**: 1207–13

Editor,—In their editorial on sedation of children by non-anaesthetists, Hatch and Sury provide good arguments for reviewing the roles and responsibilities of all those involved in the sedation of children.[1] They use their development of a nurse-led sedation service as an example of how such a review may reduce the need for immediate anaesthetic supervision.[2] For non-anaesthetists who need to sedate children, such arguments are refreshing. Unfortunately, Hatch and Sury then close with: 'Although other drugs, such as ketamine, have been used with remarkable safety, most of us [anaesthetists] would only support the use by non-anaesthetists of drugs with a margin of safety wide enough to render the loss of airway reflexes unlikely.' This suggests that ketamine should not be used by non-anaesthetists. Given the safety profile of ketamine in children[3] and the fact that laryngeal and pharyngeal protective reflexes are maintained with this drug more than with any other sedative or anaesthetic agent,[4] this final comment seems to counter their arguments for a radical review of roles and responsibilities. There are clearly training, practical and safety issues for all those involved but these need to be balanced against risks to the patient and the increasing pressure on anaesthetic, paediatric, and accident and emergency services. There is little justification for restricting the use of ketamine by appropriately trained non-anaesthetists.

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1 Hatch DJ, Sury MRJ. Sedation of children by non-anaesthetists. *Br J Anaesth* 2000; **84**: 713–14
2 Sury MRJ, Hatch DJ, Deeley T, Dicks-Mireaux C, Chong WK. Development of a nurse-led sedation service for paediatric magnetic resonance imaging. *Lancet* 1999; **353**: 1667–71
3 Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R, Hopkins GA, Garrett W, Westcott K. Intramuscular ketamine for paediatric sedation in the emergency department: safety profile in 1,022 cases. *Ann Emerg Med* 1998, **31**: 688–97
4 Drummond G. Comparison of sedation with midazolam and ketamine: effects on airway muscle activity *Br J Anaesth* 1996; **76**· 663–7

Editor,—Drs McBrien and Farling are wise to be cautious about the development of nurse-led sedation of children and we agree that this approach is not suited for small remote MRI departments. Our nurse-led service sedates approximately 800–1000 children per annum (in addition to near 450 children scanned under general anaesthesia) and aims to be self-reliant. A radiologist is nearby but the sedation nurses are likely to have much better resuscitation skills because they have regular in house training every 3 months. An anaesthetist is not available except as part of the hospital resuscitation service although anaesthetic advice or support in making decisions concerning the safety or choice of sedation is always available for the nurses. Sedation scans are allowed only during office hours.

We believe the sedation drugs we use have a margin of safety wide enough to make loss of airway and breathing reflexes unlikely but, if there was a problem, our nurses have accepted responsibility for the care of the airway and breathing. Furthermore, if the sedation protocol was not followed, for example sedating a child who had a contraindication to sedation, then the nurse would also be responsible. Other untoward events leading to appreciable morbidity or mortality are unlikely yet possible but if nurses are not trained for them they could not reasonably take any blame alone The multidisciplinary team who developed the service and who monitor its performance should share the responsibility.

For a true financial comparison of nurse- and anaesthetist-led MRI services it is important to consider the throughput of children. We agree that anaesthetists may be more efficient if they use short-acting and predictable drugs. However, we believe that sedation nurses working in partnership with anaesthetists provide a more flexible service. For example during nurse-led sessions, some children can be persuaded to lie still without sedation while others are sedated. We have been fortunate in having experienced nurses already in post whose role has been expanded. It is unrealistic to suggest that anaesthetic resources will be able to meet the increasing demand for MRI scans in a large children's unit.

We agree that quality improvement is important and we have expanded our anaesthetic services but in areas of greater need than MRI. The finding by Malviya and colleagues[1] that sedation does not keep children still reliably enough for high-quality imaging may be because they disturbed their children every 15 min during sedation to check that they were rousable. Capnography is a useful and important monitor although the sampling port may also disturb a child who is lightly asleep: we are trying new sampling tubes and reviewing our practice.

Dr Mackenzie writes, we presume, as someone who needs a suitable sedative drug for use in children by non-anaesthetists in an accident and emergency setting. We agree that ketamine has a good safety record but the quoted reference from Green and colleagues[2] reports that in a series of 1022 children aged less than 16 yr, there were four cases of laryngospasm, two of apnoea and one with respiratory depression. Although these complications were treated without intubation they do not reassure us that the drug has a margin of safety that is wide enough for use by people without anaesthetic skills.

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1 Malviya S, Voepel-Lewis T, Eldevick OP, Rockwell DT, Wong JH, Tait AR. Sedation and general anaesthesia in children undergoing MRI and CT: adverse events and outcomes. *Br J Anaesth* 2000; **84**: 743–8

2 Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R, Hopkins GA, Garrett W, Westcott K. Intramuscular ketamine for paediatric sedation in the emergency department. safety profile in 1,022 cases. *Ann Emerg Med* 1998; **31**: 688–97

The interscalene approach to the cervical plexus

Editor,—I read with interest the case report of two complications of regional anaesthesia for carotid endarterectomy.[1] Both complications occurred after deep cervical plexus block using a multiple needle technique attributed to Lofstrom [2] Stoneham and Knighton, in a review published last year,[3] favoured Winnie's single injection interscalene cervical plexus block.[4] For 15 yr, I have been using a version of Winnie's technique that, although it owes much to literary inattention, may have something to commend it in terms of safety. Reading only the summary of Winnie's paper, I believed that he was performing a standard interscalene brachial plexus block with low volume and distal pressure to encourage spread in a cephalad direction towards the cervical plexus. I have used this (accidentally modified) technique successfully since then and I can confirm that both superficial and deep elements of the plexus are reliably blocked. This continuity between the tissue spaces around the brachial and the cervical plexuses has been noted by Winnie.[5] [6] Many of the dangers of traditional approaches to the cervical plexus, i.e. both Lofstrom's and Winnie's, derive from the proximity of the tip of the needle(s) to the transverse processes of the cervical vertebrae, and therefore to dural cuffs, epidural spaces, vertebral arteries and other potentially dangerous structures. If a traditional approach to the interscalene brachial plexus is used, the needle tip should be a safe distance from those anatomical sources of danger. The upper trunks of the brachial plexus of the ipsilateral arm are, of course, blocked. Fortunately, in the context of carotid endarterectomy, it is the function of the contralateral arm that is of interest. I commend this inadvertently modified Winnie technique to your readers.

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1 Carling A, Simmonds M. Complications from regional anaesthesia for carotid endarterectomy. *Br J Anaesth* 2000; **84**: 797–800

2 Lofstrom B. Cervical nerve block. In: Eriksson E, ed *Illustrated Handbook in Local Anaesthesia*, 2nd edn. London: Lloyd-Luke, 1979, 77–8

3 Stoneham MD, Knighton JD. Regional anaesthetic for carotid endarterectomy. *Br J Anaesth* 1999; **82**: 910–19

4 Winnie AP, Ramamurthy S, Durrani Z, Radonjic R Interscalene cervical plexus block: a single injection technic. *Anesth Analg* 1975, **54**: 370–5

5 Winnie AP, Collins VJ. The subclavian perivascular anaesthetic of brachial plexus anaesthetic *Anesthesiology* 1964; **25**. 353–63

6 Winnie AP. Interscalene brachial plexus block. *Anesth Analg* 1970; **49**. 455–66

Editor,—We read with interest the recent case report by Carling and Simmonds [1] Their publication serves as a useful reminder of the potential morbidity that can result from cervical plexus local anaesthetic blockade.

It was, however, unfortunate that superficial cervical plexus block alone was not considered as a possible safe alternative.[2] This oversight would seem to continue in many UK vascular surgical units. A recent publication of a survey of UK practice revealed only 19% of vascular anaesthetists routinely employ superficial plexus blocks alone for carotid endarterectomy [3]

Superficial cervical plexus block is a recommended technique for regional anaesthesia in the neck and the need in addition for a deep cervical block has been questioned.[4] Indeed, we have found at Salisbury that performing a superficial block alone provides satisfactory anaesthesia for carotid endarterectomy (28 cases in the last 18 months). Furthermore, superficial block alone has been proven to compare well with deep cervical plexus block as part of a randomized controlled clinical trial [5] Given the potential for considerable morbidity, why bother at all with deep cervical plexus block for carotid endarterectomy?

A second point concerns Case 2. This patient was described as suffering from peripheral vascular disease and intermittent claudication that had 'recently required three pillows in bed to prevent orthopnoea'. Despite evidence of significant left ventricular dysfunction, no attempt was made to quantify or improve this before proceeding to surgery. An echocardiogram performed postoperatively showed a dilated left heart with mild/moderate mitral regurgitation and global hypokinesia. Had the patient's left ventricular function been optimized preoperatively by the addition of ACE inhibitors or diuretics, the intraoperative complications of the cervical plexus block may not have developed. As vascular patients are at particular risk of cardiac morbidity and mortality, optimization should be a priority before surgery.

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1 Carling A, Simmonds M. Complications from regional anaesthesia for carotid endarterectomy. *Br J Anaesth* 2000; **84**: 797–800

2 Masters RD, Castresna EJ, Castresna MR. Superficial and deep cervical plexus block. technical considerations. *AANA J* 1995; **63**: 235–43

3 Knighton JD, Stoneham MD Carotid endarterectomy. A survey of UK anaesthetic practice. *Anaesthesia* 2000; **55**: 475–88
4 Pinnock CA, Fischer HBJ, Jones RP. *Peripheral Nerve Blockade*. New York: Churchill Livingstone, 1996; 48
5 Stoneham MD, Doyle AR, Knighton JD, Dorje P, Stanley JC. Prospective, randomised comparison of deep or superficial cervical plexus block for carotid endarterectomy surgery. *Anesthesiology* 1998; **89**: 907–12

Editor,—Thank you for the opportunity to reply to the letters from Drs Harrop-Griffiths and Cockroft and Brownlow. Having experienced two significant adverse sequelae to our regional anaesthetic technique we are only too keen to question ourselves. We were interested to read of Harrop-Griffiths' successful approach to blocking the cervical plexus with a modified single injection interscalene brachial plexus block. Winnie's technique[1] involves a single interscalene injection of a small volume of local anaesthetic to the level of C4 with distal pressure being applied to prevent caudad spread to the brachial plexus and deliberately encourage cephalad spread to the cervical plexus. (We do not believe he was describing a modified brachial plexus block as such to block the cervical plexus.) Nonetheless the interscalene brachial plexus block with a single injection is not without hazard and it is still possible to inadvertently cause an epidural or subarachnoid block or accidental injection into the vertebral artery with this approach.[2–6] Even if local anaesthetic solution is not directly injected into the vertebral artery there is a suggestion that a bolus of local anaesthetic lying in close proximity to the vertebral artery may cause rapid absorption and cerebral toxicity.[7] The 'heavy arm' that may result from an unwanted ipsilateral brachial plexus block although neurologically not the focus of interest during a carotid endarterectomy is still of nuisance value, particularly postoperatively.

In the Royal Gwent Hospital a combined deep and superficial cervical plexus block has been used in 81 patients undergoing carotid surgery over 3 yr. We agree that it is still unclear as to whether superficial cervical plexus block alone is superior to a combined superficial and deep block. Placement of the needle using a nerve stimulator (which was the technique used in both of our case reports) is reported to produce a more effective block and from our experience is superior to eliciting paraesthesia which the patient may find difficult to differentiate from pain.[8] It is entirely plausible that a small amount of local anaesthetic injected accurately at three levels with a nerve stimulator will produce a highly effective and safe block and that this is potentially safer and superior to a large volume injected at one site using a single injection technique. Unfortunately there is no real evidence to clarify this. Using our combined technique, between 0 and 5 ml of 0.5% lidocaine is used as a supplement by the surgeon. Similarly to Stoneham and Knighton, we have observed an intraoperative seizure in one patient who received a minimal top-up and this led to the procedure being abandoned.[7] There is a suggestion that more local anaesthetic supplementation is required to achieve a comfortable and successful superficial cervical blockade: this in itself could increase the risk of cerebral toxicity[7] From our experience, patients who have an inadequate block are restless and difficult to settle intra-operatively and i.v. fentanyl is not helpful. We also recall two patients who needed to return to theatre for re-exploration following carotid surgery. As they had received an effective deep and superficial cervical plexus block at the time of the original surgery it was possible to immediately proceed with the re-exploration with minimum local anaesthetic supplement; thus a general anaesthetic was avoided. Superficial blockade may be a preferable technique for patients with respiratory disease but we make no apology for repeating the conclusions of Stoneham and Knighton: it remains unclear whether superficial blockade alone is superior to a combined technique.[9 10]

The second case clearly demonstrates that patients undergoing carotid endarterectomy suffer considerable comorbidity. Despite optimizing the patients' physical condition prior to surgery, there are still risks of cardiorespiratory failure. It should be emphasized that these patients are urgent cases suffering symptomatic disease often on the brink of having a stroke and time for perioperative medical optimization can be limited, especially if a change in long-term medication is needed. Cancellation carries a risk.

Due to the small number of patients studied in previous trials, we will all have to wait to see if any future studies can elucidate the best way to anaesthetize patients for carotid endarterectomy.[10] Meanwhile, we believe we must all be aware of the complications that can beset us when using any local anaesthetic technique for this procedure.

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1 Winnie AP, Ramamurthy S, Durrani Z, Radonjic R. Interscalene cervical plexus block: a single-injection technic. *Anesth Analg* 1975; **54**: 370–5
2 Scammell SJ. Inadvertent epidural anaesthesia is a complication of interscalene brachial plexus block. *Anaesth Intens Care* 1979; **7**: 56–7
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4 Norris D, Klahsen A, Milne B. Delayed bilateral spinal anaesthesia following interscalene brachial plexus block. *Can J Anaesth* 1996; **43**: 303–5
5 Ross S, Scarborough CD. Total spinal anaesthesia following brachial-plexus block *Anesthesiology* 1973; **39**: 458
6 Mulroy MF, Thompson GE. Interscalene approach. In. Hahn MB, McQuillan PM, Sheplock GJ, eds. *Regional Anaesthesia. An Atlas of Anatomy and Techniques*. USA: Mosby, 1996; 95–9
7 Stoneham MD, Knighton JD. Transient ischaemic attack during deep cervical plexus block. *Br J Anaesth* 1999; **83**: 966
8 Mehta Y, Juneja R. Regional analgesia for carotid artery endarterectomy by Winnie's single injection technique using a nerve detector. *J Cardiovasc Anesth* 1992; **6**: 772–3
9 Stoneham MD, Knighton JD. Regional anaesthesia for carotid endarterectomy. *Br J Anaesth* 1999; **82**: 910–19
10 Stoneham MD, Knighton JD. Efficacy and safety of the superficial cervical plexus block for carotid endarterectomy *Br J Anaesth* 1999; **83**: 971–2

Nitric oxide concentration in the presence of potent inhalation anaesthetics

Editor,—In their recent investigation Liu and colleagues[1] demonstrated that in the presence of potent inhalational anaesthetics, nitric oxide (NO) concentration measured by chemiluminescence decreased with increasing concentrations of the potent anaesthetic agent. The authors conclude that the underestimation in the NO reading results at least in part from emission absorption and possibly also from the quenching phenomenon, but they do not provide conclusive evidence for the effect of either mechanism. However, they clearly show that a chemical reaction between the inhalational anaesthetic agents and NO can be excluded.

It is well known from a series of investigations that specific mixtures of carrier gas can influence NO measurement by chemiluminescence. According to Tidona and colleagues[2] and Liu[1] several mechanisms should be considered when using chemiluminescence for NO measurements: (i) in the reaction chamber: collisional deexcitation (so-called quenching), emission absorption, possible chemical reaction between the nitrogen oxides and the interfering gas component in question, e.g. volatile

Table 1. Ratio between carrier gas and reference gas flow calculated from the inlet flow sampled by the chemiluminescence analyser ML9841A
*iso = isoflurane, §oxygen as reference gas

Gas	O_2/N_2	Air/N_2	$Argon/N_2$	N_2O/N_2	5% iso* in 95% N_2/N_2	$Carbogen/O_2$§
Ratio	0.930	0.982	0.870	0.804	0.875	0.988

anaesthetics; and (ii) the number of NO molecules entering the reaction chamber per unit time. As mentioned above, Liu and colleagues[1] have convincingly ruled out a chemical reaction.

With regard to emission absorption, Liu[1] speculates that the underestimation of NO concentration in their experiments may be due to absorption of the NO_2* (electrically excited NO_2) emissions by the potent inhalational anaesthetics. The problem with this suggestion is that the emission wavelength of NO_2* lies in a range of 600–3000 nm[2] with a peak at 1100–1200 nm. To our knowledge, volatile anaesthetics have four absorption bands in the infrared range of the spectrum. Two bands (around 3300 nm and 7000–15 000 nm) lie beyond the range of the emission wavelength of NO_2* and are thus not relevant. The band around 1690 nm is not only weaker than the two others, it, too, is distant from the NO_2* emission peak. The fourth absorption band of the anaesthetics around 1140 nm coincides with the NO_2* peak emission wavelength. However, besides being the weakest band, it is very narrow, namely with a half-width of about 2 nm. Peak absorption of e.g. halothane and desflurane at a concentration of about 5% is only 0.3% of the incident light in an optical cell of 10-cm path length (H.-D. Hattendorf, Drägerwerk AG, Lübeck, Germany, personal communication). It is difficult to believe that this very low absorption could explain Liu's findings.[1] But even more important is that the red-sensitive photomultiplier tube in the Sievers nitric oxide analyser responds to the regions between 600 and 900 nm only (R. Hutte, Sievers Instruments, Boulder, CO, USA, personal communication). Thus, it appears that emission absorption by the inhalational anaesthetics can be ruled out as an explanation of the findings of Liu's paper.

The quenching phenomenon mentioned by Liu[1] has been investigated by Tidona and colleagues[2], van der Mark and colleagues[3] and Zabielski and colleagues[4] in more detail. Basically, by decreasing the probability of collisional de-excitation, quenching can be reduced. This is the reason why several commercial analysers operate with very low reaction-chamber pressures.[2 4] However, a certain amount of quenching is generally unavoidable. As there are no data on quenching by inhalational anaesthetic agents, we agree with Liu[1] that further investigation is warranted in this connection.

We believe there is a more convincing explanation for the results found. The sample flow into the chemiluminescence analysers determines the number of NO molecules entering the reaction chamber per unit time. Flow constancy in these analysers is achieved by either a critical orifice or a capillary. When we measured the gas flow of different carrier gases sampled by our chemiluminescence analyser (ML9841A; Monitor Labs, Englewood, CO, USA), we found that the sample flow rate changed depending on the carrier gas composition (see Table 1). Notably, a decrease of about 13% in the sample flow rate was observed when we sampled 5% isoflurane in nitrogen. Unfortunately, with our analyser we were not able to measure NO in the presence of isoflurane for the same reason as mentioned by Schedin and colleagues,[7] i.e. the permanent loss of converter efficiency after exposing the converter to isoflurane.

In addition, when nitric oxide was added to the carrier gas and the latter was changed from N_2 to O_2, the decrease in the NO concentration indicated by our chemiluminescence analyser correlated very closely both with the measured (decreased) gas flow and the calculated (theoretical) value.[5 6] In summary, when the composition of the carrier gas changes, its viscosity changes, and so the sample gas flow into the analyser must also change.[2 4 5]

Though not considered relevant by other authors,[8–10] our own conclusion is that a factor as simple as a change in gas flow into the reaction chamber may be responsible for inaccurate readings of NO concentration. We feel that reduction in gas flow should be definitively ruled out as the cause of the low readings observed by Liu[1] before further speculation about factors intrinsic to chemiluminescence is pursued.

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1 Liu R, Ishibe Y, Okazaki N, Kimura K. Chemiluminescence underestimates nitric oxide concentration in the presence of potent inhalation anaesthetics. *Br J Anaesth* 2000; **84**: 596–9
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4 Zabielski MF, Seery DJ, Dodge LG. Influence of mass transport on quenching of nitric oxide chemiluminescent analysis. *Environ Sci Technol* 1984, **18**: 88–92
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6 Bohl W. *Technische Stromungslehre*, 10th edn. Würzburg. Vogel Buchverlag 1994; 208–12
7 Schedin U, Frostell CG, Gustafsson LE. Formation of nitrogen dioxide from nitric oxide and their measurement in clinically relevant circumstances. *Br J Anaesth* 1999; **82**: 182–92
8 Etches P, Harris M, McKinley R, Finer N. Clinical monitoring of inhaled nitric oxide: comparison of chemiluminescent and electrochemical sensors. *Biomed Instrum Technol* 1995; **29**: 134–40
9 Fajardo CA, Prokopowich J, Belik J. Inhaled nitric oxide monitoring. *Clin Invest Med* 1995, **18**: 114–21
10 Francoe M, Troncy E, Blaise G. Inhaled nitric oxide: technical aspects of administration and monitoring. *Crit Care Med* 1998; **26**: 782–95

Editor,—We thank Drs Milovic and Gilly for their valuable comments concerning the discussion in our paper[1] about the mechanisms of the underestimation of nitric oxide (NO) measured by chemiluminescence in the presence of potent inhalational anaesthetics. We are also glad to have the opportunity to reply.

For their comment about emission absorption, we agree with their opinion that it appears that emission absorption by inhalational anaesthetics can be ruled out as an explanation of the underestimation of the NO concentration, because there is no emission absorption at 600–900 nm wavelength with potent inhalational anaesthetics.

The question regarding the flow into the reaction chamber is important. Although we agree that a change in the sample flow rate may occur due to a change in gas composition, we do not believe that the decrease in the flow in this range is the (main) cause for the underestimation of NO. During our recent investigation using a NO analyser (model 280, Software Version 2.05, Sievers Instruments Inc., Boulder, CO) with a 200 ml min^{-1} porous metal flow restrictor, we also found that the sample flow rate decreased from 200 ml min^{-1} to 150–160 ml min^{-1} when the concentration of sevoflurane increased from 0% to 4% in N_2. According to the analyser service manual, the actual flow into the analyser will depend on the gas composition; however, as long as the flow is maintained in the range of 150–250 ml min^{-1} when a standard flow restrictor (200 ml min^{-1}) is used, the gas flow change originating from the change in gas composition will not affect the response of the analyser.

If the decrease in sample flow rate is the cause of the underestimation, the extent of the underestimation can be corrected by control of the flow rate. However, in our recent laboratory investigations, when the sample flow rate was kept at a constant level (200 ml min^{-1}) by a mass flow controller, underestimation still occurred in a similar manner, indicating that a decrease in flow is not the cause of the underestimation.

Furthermore, no reaction between NO (or NO_2) and potent inhalational anaesthetics was observed in our latest laboratory investigation using infrared absorption spectroscopy. We believe that most of the underestimation of NO concentration in the presence of potent inhalational anaesthetics is due to quenching. We are preparing the new findings related to this quenching phenomenon for publication.

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Anaesthesia, jugular venous oxyhaemoglobin saturation and coronary artery bypass surgery

Editor,—We welcome the paper by Nandate and colleagues[1] not least because it confirms our descriptions of low levels of jugular bulb oxyhaemoglobin saturation ($S\mathrm{j}_{O_2}$), using both continuous and discrete measurements in the early postoperative period following coronary artery bypass grafting (CABG) surgery,[2 3] but also because it confirms our suspicion that anaesthesia has an important influence upon $S\mathrm{j}_{O_2}$ at this time. However, we are concerned that one very important factor has neither been reported in their paper nor taken into account in the statistical analysis. We reported that arterial carbon dioxide tension (Pa_{CO_2}) is a very important determinant of $S\mathrm{j}_{O_2}$ during and after CABG surgery and should therefore always be taken into account when examining $S\mathrm{j}_{O_2}$ in this setting.[2] Whilst they have stated that alpha-stat acid base management was employed during cardiopulmonary bypass, in reality Pa_{CO_2} may vary considerably between patients during this period and so may have had a marked effect upon $S\mathrm{j}_{O_2}$. If, as we have described,[2] Nandate and colleagues had included Pa_{CO_2} in their analysis of variance for repeated measures as a varying covariate, the true between-group differences could either be greater or less than the values they have reported. Information regarding the application of, and weaning from, mechanical ventilation would also have been valuable as this might also have important influences upon arterial Pa_{CO_2} and thus $S\mathrm{j}_{O_2}$.[4] Knowledge of Pa_{CO_2} becomes even more important when attempting to unravel the relationship between levels of $S\mathrm{j}_{O_2}$ during and after CABG surgery to neurological and cognitive outcome. We therefore wish to reiterate our plea,[2] that if meaningful interpretation of $S\mathrm{j}_{O_2}$ is to be made, at the very minimum levels of Pa_{CO_2} should be provided in future studies and, ideally, they should be included in any statistical analysis.

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1 Nandate K, Vuylsteke A, Ratsep I, *et al* Effects of isoflurane, sevoflurane and propofol anaesthesia on jugular venous oxygen saturation in patients undergoing coronary artery bypass surgery. *Br J Anaesth* 2000; **84**: 631–3
2 Millar SA, Alston RP, Souter MJ, Andrews PJD. Aerobic, anaerobic and combination estimates of cerebral hypoperfusion during and after cardiac surgery. *Br J Anaesth* 1999; **83**: 936–9
3 Souter MJ, Andrews PJD, Alston RP. Jugular venous saturation following cardiac surgery. *Br J Anaesth* 1998; **81**: 239–41
4 Liau SS, Alston RP, Robson MJA. Jugular bulb oxyhaemoglobin saturation after cardiac surgery: effect of weaning from mechanical ventilation. *Br J Anaesth* 2000, **84**: 275–6P

Editor,—We would like to thank Dr Alston and colleagues for their interest in our manuscript. We agree that Pa_{CO_2} has to be taken into account when analysing $S\mathrm{j}_{O_2}$ data. In our study, alpha-stat acid based management was employed and Pa_{CO_2} did not significantly affect $S\mathrm{j}_{O_2}$ at any time point using MANOVA with Pa_{CO_2} and anaesthetic agents as independent variables, and $S\mathrm{j}O_2$ as the dependent variable. We include the Pa_{CO_2} values for completeness (Table 1).

Table 1. Pa_{CO_2} (mean (SD))

Time point	Isoflurane	Sevoflurane	Propofol
T0	5.23 (0.5)	5.22 (0.5)	5.87 (0.8)
T1	5.75 (0.6)	4.87 (0.9)	5.53 (0.9)
T2	5.89 (0.5)	5.66 (0.5)	5.68 (0.9)
T3	4.99 (1)	5.47 (0.7)	5.55 (0.9)
T4	5.5 (0.7)	5.32 (1)	5.79 (0.6)
T5	5.65 (0.5)	5.68 (0.7)	5.61 (0.7)
T6	5.67 (0.8)	6.61 (0.74)	6.41 (0.5)

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Spinal cord injury and direct laryngoscopy–the legend lives on

Editor,—I congratulate McLeod and Calder on their excellent editorial[1] and agree with them wholeheartedly that too much emphasis is placed on the danger of spinal cord injury following direct laryngoscopy. They also stress that the key issue for both the brain and spinal cord is maintenance of perfusion and hence tissue oxygenation. Even brief episodes of hypoxia and hypotension are known to adversely affect outcome after head injury.[2]

In 1991, I analysed the reason for admission of 150 trauma patients cared for in the Major Injuries Unit of Birmingham Accident Hospital. A total of 100 patients had a head injury and 10 had a cervical spine injury. Of these, only eight patients had a co-existing head and cervical spine injury. Our records did not allow me to identify how many patients underwent laryngoscopy prior to clearance of the cervical spine. Some, however, certainly did. The Birmingham Accident Hospital was unusual because, unlike most accident and emergency departments, only trauma and burns patients were admitted. Hence the anaesthetists treated a higher proportion of injured patients than might be expected in most city hospitals. There were four trainees and three consultants who were usually present for major trauma admissions. Assuming an even distribution of patients between these seven anaesthetists, each could expect to see one combined head and spinal injury and approximately 13 isolated head injury patients each year. Even though the data are 'soft', this illustrates the relative rarity of spinal cord injury compared to head injury.

I wonder how many head injured patients are subjected to a period of ischaemia while an anaesthetist struggles to visualize the larynx with the neck stabilized either in a collar, by manual in-line traction, or by another of the recommended techniques?

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1 McLeod ADM, Calder I. Spinal cord injury and direct laryngoscopy—the legend lives on. *Br J Anaesth* 2000, **84**: 705–9
2 Chesnut RM, Marshall LF, Klauber MR, *et al.* The role of secondary brain injury in determining outcome from severe head injury. *J. Trauma* 1993; **34**: 216–22

Editor,—We thank Dr Sutcliffe for her kind comments. We agree that measures intended to make direct laryngoscopy safer in patients with disease of the cervical spine should be implemented in an informed manner. This group of patients runs a risk of neurological deterioration during the perioperative period, but the causation is unlikely to be as satisfyingly simple as a 'crunch' during laryngoscopy.

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Randomized controlled comparison of epidural bupivacaine versus pethidine for analgesia in labour

Editor,—I was interested to read the article by Loughnan and colleagues.[1] Their conclusion was that there was no increased incidence of Caesarean section associated with epidural analgesia in a standardized actively managed labour. But this conclusion was based on a statistical hypothesis rather than actual facts.

Looking at Table 3, it is obvious that the assisted and Caesarean section deliveries were considerably higher in patients who were randomized to accept epidural analgesia compared to pethidine (43 *vs* 31%). This 12% difference might not be significant in statistical terms but it could be of significance in a clinical setting. Seventy per cent of 166 patients who opted out of the study had either assisted or Caesarean section delivery. From Fig. 1, I found 112 of these patients received epidural analgesia. It would be interesting to know how many of these 112 patients underwent assisted or Caesarean section delivery compared to 54 patients who managed without an epidural.

While conducting this kind of study it is difficult to eliminate bias in terms of randomization; quality of care and clinical decisions; high percentage drop-out rate; or degree of blindness. The patients in this trial[1] were selected on the basis of strict criteria and all of them received standardized obstetric care The methods of analgesia provided to them were based on maternal request rather than on any medical or obstetric indication. Thus, they could be divided into three groups based on what they finally received for labour analgesia. One group of 194 patients received Entonox. The second group of 432 patients received epidural analgesia and the remaining 176 patients received only pethidine. It would be useful to calculate the incidence of assisted and/or Caesarean section delivery rate in these groups. Alternatively, a comparative figure of instrumental deliveries could be drawn between the two randomized groups who received epidural analgesia (235 patients) and pethidine analgesia (128 patients). I would also like to know the incidence of assisted delivery and Caesarean section in those 188 patients who were not randomized and received Entonox or no analgesia.

It is well established that an epidural provides superior quality of analgesia in labour.[2] However, it obtunds physiological reflexes and reduces motor function, depending upon the concentration and type of local anaesthetic agents used Various studies have shown that an epidural does increase the incidence of instrumental delivery including Caesarean section, and also prolongs the duration of labour.[2 3] Lower concentrations of local anaesthetics along with opioids have shown a reduction in instrumental deliveries.[4 5] The implication from these studies[4 5] is that there is an association between the use of local anaesthetics and instrumental deliveries.

This study[1] may prove that epidural analgesia does not increase the incidence of Caesarean section delivery in statistical terms but this may not be true in the clinical setting. Further investigation is required in order to establish the influence of epidural analgesia on instrumental deliveries.

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1 Loughnan BA, Carli F, Romney M, Dore CJ, Gordon H. Randomized controlled comparison of epidural bupivacaine *versus* pethidine for analgesia in labour. *Br J Anaesth* 2000; **84** 715–9
2 Halpern SH, Leighton BL, Ohlsson A, Barrett JFR, Rice A. Effect of epidural vs parenteral opioid analgesia on the progress of labor. *JAMA* 1998; **280**· 2105–10
3 Thorp JA, Hu DH, Albin RM, McNitt J, Meyer BA, Cohen GR, Yeast JD. The effect of intrapartum epidural analgesia on nulliparous labor. a randomized controlled prospective trial. *Am J Obstet Gynecol* 1993; **169**: 851–8

4 Olofsson CH, Ekblom A, Ekman-Oreberg G, Irestedt L. Obstetric outcome following epidural analgesia with bupivacaine–adrenaline 0.25% or bupivacaine 0.125% with sufentanil – a prospective randomized controlled study in 1000 parturients. *Acta Anaesthesiol Scand* 1998; **42**: 284–92

5 James KS, McGrandy E, Quasim I, Patrick A. Comparison of epidural bolus administration of 0.25% bupivacaine with 0.0002% fentanyl for analgesia during labour. *Br J Anaesth* 1998; **81**: 507–10

Editor,—Thank you for the opportunity to respond to Dr Mandal. We do not agree that the use of an intention to treat analysis is a statistical hypothesis, rather we consider that it is the only unbiased way of analysing the data. Most recent studies attempting to establish the effects of epidural analgesia on the progress of labour and delivery use this approach. In their systematic review, Howell and Chalmers[1] criticized a number of studies where an intention to treat analysis had not been used.

Table 1 (see facing page) contains comparisons on the basis of analgesia received for all 802 women who agreed to participate in our trial at the start of labour. There are significant trends with increasing analgesia for 16 of the 23 variables tested. There is a marked increase in Caesarean section rate in mothers who received an epidural (15%) or an epidural plus pethidine (23%). However, these women were more likely also to have had an induced labour, tended to be heavier, had larger babies, had longer labours, etc. It is impossible to disentangle cause from effect. We must emphasize that this is a biased method of analysis and illustrates the pitfalls inherent in such an approach.

We performed a randomized study and have therefore used a method of analysis appropriate to this, which is the intention to treat analysis. Had we chosen to present our findings on the basis of treatment received, we would simply have been reporting a randomized trial as if it were an observational study.

We consider that the use of randomization eliminates much of the bias due to quality of care and clinical decisions. The method of analgesia offered was based on randomization not on maternal request. The major drawback of our study is the high drop out rate and we could not dictate at what stage mothers chose to opt out. Some mothers on discovering that they were assigned to an epidural/pethidine then opted in favour of the treatment they actually preferred.

Although epidural analgesia does have an effect on physiological reflexes, the use of an active management protocol for labour largely negates this. Halpern[2] in his meta-analysis supports our contention that epidural analgesia does not of itself increase the Caesarean section rate Thorp and colleagues[3] found an increase in Caesarean section rate with epidural analgesia, but other more recent studies involving larger numbers[4 5] of women have failed to replicate their findings.

The studies comparing low dose local analgesia with opiates suggest a possible contributory role of the concentration of local analgesic. However, our study was designed to assess the effect of epidural analgesia alone on the Caesarean section rate. We referred in our paper to the fact that modern practice is to use a lower concentration of local analgesic. If anything we should be even more confident in assuring mothers who are receiving lower concentrations of epidural local analgesics that their chances of having a Caesarean section are not increased.

We agree that in the clinical setting epidural analgesia may be associated with a higher incidence of Caesarean delivery However, this may be due to factors such as the labour itself or maternal factors rather than the epidural *per se*. A woman who is experiencing problems with her labour is more likely to request an epidural. Our study using an intention to treat analysis and standardized management of labour shows that the use of epidural analgesia of itself is not associated with an increase in Caesarean section rate. Our findings are in agreement with those of other groups using a similar design and analysis.

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1 Howell CJ, Chalmers I. A review of prospectively controlled comparisons of epidural with non-epidural forms of pain relief in labour. *Int J Obstet Anesth* 1993; **2**: 15–20

2 Halpern SH, Leighton BL, Ohlsson A, Barrett JFR, Rice A. Effect of epidural vs parenteral opioid analgesia on the progress of labor. *JAMA* 1998; **280**: 2105–10

3 Thorp JA, Hu DH, Albin RM, McNitt J, Meyer BA, Cohen GR, Yeast JD. The effect of intrapartum epidural analgesia on nulliparous labor: a randomized controlled prospective trial. *Am J Obstet Gynecol* 1993; **169**: 851–8

4 Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG. A randomised trial of epidural versus patient-controlled meperidine analgesia during labor. *Anesthesiology* 1997; **87**: 487–94

5 Ramin SM, Gambling DR, Lucas MJ, Sharma SK, Sidawi JE, Leveno KJ. Randomized trial of epidural versus intravenous analgesia during labor. *Obstet Gynecol* 1995; **86**: 783–9

Propofol with and without nitrous oxide

Editor,— We read with interest the paper of Stuart and colleagues[1] describing their determination of the calculated Cp50 of propofol. Using classic methodology, the authors reported that the calculated Cp50 of propofol was 6.8 $\mu g\ ml^{-1}$ (95% confidence limits: 6.7–6.9 $\mu g\ ml^{-1}$) in patients breathing oxygen and air.

Propofol blood concentrations in this study were calculated *not* measured. The Cp50 of propofol has been estimated at least twice before, using arterial blood sampling to determine actual propofol concentrations, and the value was ~15 $\mu g\ ml^{-1}$.[2 3] When the Cp50 is estimated using venous sampling, or is measured in the presence of other drugs, the value is substantially less [2 4]

Why was the Cp50 value calculated by Stuart only half the previously reported values? They used: similar fit, healthy, non-obese patients for their study, who had received no other drugs; a computer-controlled infusion which is capable of producing and maintaining constant propofol blood concentrations; and allowed sufficient time for equilibration with the effect site. A standard supramaximal stimulus was applied and the response assessed by a blinded observer.

The answer must be that the computer-controlled infusion over-achieved the target substantially at the concentrations targeted in this study. This device is known to produce measured concentrations which are in general greater than those targeted. The greater the target, the greater the potential upwards divergence of the measured value.[5] This is likely due to the haemodynamic effects of propofol. Whilst the predictive performance of the Diprifusor is clinically acceptable, and similar to other devices, the calculated Cp50 values are likely to be underestimates of the true value.

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1 Stuart PC, Stott SM, Millar A, Kenny GNC, Russell D Cp50 of propofol with and without nitrous oxide 67%. *Br J Anaesth* 2000; **84**: 638–9

Table 1. Comparison of all women who consented at the start of labour by treatment received. Summary statistics are mean (SD) for variables analysed by ANOVA orthogonal contrast test for trend, median (interquartile range) for variables analysed by Cuzick's non-parametric test for trend, and frequencies (%) for variables analysed by Chi squared test for trend

Variable	**Epidural + pethidine ($n = 99$)**		**Epidural ($n = 333$)**		**Pethidine ($n = 176$)**		**Minimal analgesia ($n = 194$)**		***P* value**
Randomized treatment Epidural	13/99	(13%)	244/333	(73%)	44/176	(25%)	3/194	(2%)	
Pethidine	86/99	(87%)	89/333	(27%)	132/176	(75%)	3/194	(2%)	
Not randomized	0/99	(0%)	0/333	(0%)	0/176	(0%)	188/194	(97%)	
Age, yr	26.7	(00–00)	27.2	(00–00)	25.9	(00–00)	26.6	(00–00)	0.4
Final weight, kg	77	(68–87)	74	(67–84)	74	(67–80)	73	(65–82)	0.01
Height, cm	161.9	(6.2)	162.2	(6.6)	162.8	(6.3)	162.5	(6.5)	0.3
Married	62/99	(63%)	239/332	(72%)	114/176	(65%)	134/194	(69%)	0.9
Caucasian	64/97	(66%)	197/332	(59%)	103/174	(59%)	122/194	(63%)	1.0
Social class I/II/III	73/95	(77%)	250/327	(76%)	121/171	(71%)	134/183	(73%)	0.3
Induced	30/97	(31%)	108/330	(33%)	47/175	(27%)	37/193	(19%)	0.002
First stage, h	10.7	(8.6–12.7)	9.2	(7.0–12.3)	6.8	(4.8–9.4)	5.9	(3.9–8.0)	<0.001
Second stage, h	1.7	(0.8–2.5)	1.6	(0.8–2.4)	0.8	(0.5–1.3)	0.7	(0.3–1.1)	<0.001
First treatment to full dilatation, h	5.8	(4.0–8.1)	4.0	(2.3–6.2)	1.8	(1.0–3.0)	1.5	(0.8–2.7)	<0.001
Entonox	72/98	(73%)	205/332	(62%)	153/176	(87%)	161/194	(83%)	<0.001
Oxytocin	78/99	(79%)	229/333	(69%)	53/174	(30%)	37/191	(19%)	<0.001
Mode of delivery									
Normal vaginal	32/99	(32%)	172/333	(52%)	161/176	(91%)	173/194	(89%)	<0.001
Instrumental vaginal	44/99	(44%)	110/333	(33%)	13/176	(7%)	19/194	(10%)	
Caesarean	23/99	(23%)	51/333	(15%)	2/176	(1%)	2/194	(1%)	<0.001
Gest. age, weeks	40	(39–41)	40	(39–41)	40	(39–41)	40	(39–41)	<0.001
Fetal wt, kg	3.4	(3.2–3.7)	3.3	(3.0–3.7)	3.3	(2.9–3.6)	3.2	(2.8–3.5)	<0.001
Apgar 5m <9	0/99	(0%)	9/331	(3%)	8/176	(5%)	5/193	(3%)	0.4
Pain relief stage 1 excellent/good	35/92	(38%)	252/300	(84%)	86/147	(59%)	110/160	(69%)	0.2
Pain relief stage 2 excellent/good	42/59	(71%)	237/279	(85%)	83/144	(58%)	95/149	(64%)	<0.001

2 Smith C, McEwan A, Jhavieri R, *et al.* Interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. *Anesthesiology* 1994; **81**. 820–8

3 Andrews DT, Leslie K, Sessler DI, Bjorksten AR. The arterial blood propofol concentration preventing movement in 50% of healthy women after skin incision. *Anesth Analg* 1997; **85**: 414–9

4 Davidson JAH, Macleod AD, Howie JC, White M, Kenny GNC. Effective concentration 50 for propofol with and without 67% nitrous oxide. *Acta Anaesthesiol Scand* 1993, **37**: 458–64

5 Swinhoe CF, Peacock JE, Glen JB, Reilly CS. Evaluation of the predictive performance of a Diprifusor TCI system. *Anaesthesia* 1998; **53** (Suppl 1)· 61–7

Editor,—Thank you for the opportunity to reply to the letter by Drs Leslie and Andrews. The question of what represents the true concentrations within the pharmacokinetic model during an infusion of propofol can be considered in several ways since there are many different factors which will affect the relationship between the calculated and the predicted values. It is important to realize that a 3-compartment pharmacokinetic model predicts the concentration within the central compartment of the model. Blood is taken to represent the central compartment but, in the case of propofol, the blood volume is about 1/3 of the volume of the central compartment.

Blood samples obtained synchronously from different sites within the vascular system can give widely different values. Major and his colleagues[1] took simultaneous blood samples from an artery, a peripheral vein and a central vein and measured the propofol concentrations. Up to 60 s after the end of administration of the drug there were wide differences in drug concentrations between the sampling sites. However, from 60 s after the end of dosing, there were no significant differences in drug concentrations between the three sites. Their conclusion was that, as long as this mixing period was allowed for, peripheral venous sampling provides an acceptable alternative to arterial puncture in studies to correlate drug effect and concentration and for pharmacokinetic investigations.

If blood samples are withdrawn during infusion at high flow rates then adequate mixing of the drug may not have occurred and abnormally high values of drug concentration may be measured, which reflect this inadequate mixing.[2 4] Many of the anomalies in recording drug concentration during drug infusion compared with during zero infusion can be explained by the fact that any model assumes instantaneous mixing of the drug within the central compartment and clearly this is impossible.

Assume that a target blood concentration of 6 $\mu g\ ml^{-1}$ is selected for a patient weighing 70 kg. The infusion pump will deliver propofol 1% at approximately 120 $ml\ h^{-1}$ after the initial bolus dose. This is 2 $ml\ min^{-1}$ or 20 000 $\mu g\ min^{-1}$. If the patient has a cardiac output of 5000 $ml\ min^{-1}$, then each ml of blood will transfer 4 µg to the central compartment to replace that lost by redistribution and metabolism from the central compartment. Therefore, to maintain a blood concentration of 6 $\mu g\ ml^{-1}$, the arterial blood must contain 10 $\mu g\ ml^{-1}$ during the period of rapid infusion. The bias for the drug concentration in the blood sample would then be positive compared with that predicted by the model for the central compartment. If, however, the rapid infusion is stopped and the system is left for 60–90 s, then the system will have time to equilibrate and the blood will have approximately the same concentration as the central compartment and the bias will be about zero. But, since the blood volume for propofol is only about 1/3 of the volume of the central compartment, it will take a relatively long time for the drug to mix completely within the central compartment. Swinhoe and colleagues reported a bias of 16.2% in their simultaneous comparison of blood and predicted propofol concentrations using the 'Diprifusor' TCI system.[5] This compares favourably with the study by Davidson and his colleagues who reported a bias of 25.6% during drug infusion. However, the bias decreased to 0.4% when the infusion had been discontinued for at least 90 s.[4] This illustrates the importance of allowing time for equilibration between the blood and the central compartment before using the blood concentration to represent the concentration within the central compartment.

In addition, the individual values of prediction error for each blood sample may vary considerably throughout the course of drug administration, partly because of acute changes in physiology that occur on exposure to different blood concentrations of drug (dose dependent pharmacokinetics). Within any patient population, even those who are matched with respect to age, weight and sex, there may be additional pharmacokinetic variability.

In their study investigating propofol Cp50 for measured arterial concentration, Andrews and colleagues used a target controlled infusion system incorporating a different pharmacokinetic model from that contained in 'Diprifusor' TCI systems.[6] They found close correlation between target concentration and measured arterial blood concentration *during infusion*, but did not sample with the system during zero infusion rate. Had they done so we believe that the measured arterial concentration would have been significantly lower than the calculated concentration. We believe that to achieve an arterial concentration of 15 $\mu g\ ml^{-1}$ during infusion using 'Diprifusor' TCI would require a target concentration of about 9 $\mu g\ ml^{-1}$, which is closer to our $Cp50_{CALC}$ value of 6.8 $\mu g\ ml^{-1}$. The value for $Cp50_{CALC}$ which we reported was close to the calculated value reported by Davidson and colleagues[4] in a similar group of patients who had received benzodiazepine premedication, and we believe it represents a realistic view of the dynamic changes in pharmacokinetics during a propofol infusion.

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Inhalation sedation with sevoflurane for upper gastrointestinal endoscopy

Editor,—Upper gastrointestinal endoscopy may be performed without sedation, but many patients find this unacceptable and worry about further examination.[1] The use of sedation is thought to produce better conditions for examination;[2] patient discomfort is less and acceptance of the procedure is better. Sevoflurane is a non-pungent inhalational anaesthetic agent with a low blood/gas solubility coefficient, with properties which allow rapid induction and emergence.[3] It has a minimum alveolar concentration (MAC) of approximately 2%. Its MAC-awake, the end-tidal concentration permitting voluntary response to command in 50% of patients, is about one third MAC.[4] Sevoflurane may therefore be a potent amnesic. In a preliminary study, we assessed the efficacy, safety and feasibility of using sevoflurane as an inhalational sedation for patients during upper gastrointestinal endoscopy.

After obtaining approval from the Hospital Ethics Committee and written informed consent, we studied 30 adult patients, ASA I or II, aged 18–70 yr, undergoing day-case diagnostic upper gastrointestinal endoscopy. Exclusion criteria included severe impairment of cardiorespiratory function, patients who were taking sedative medication, those who were pregnant and those who had previous adverse reactions to sevoflurane. Prior to sedation and endoscopy, all patients had pharyngeal anaesthesia with lidocaine spray 10% (10 squirts = 100 mg). Patients were also asked to evaluate their 'fear' of the procedure using a 0–10 cm visual analogue score (VAS) before the start of the procedure and after completion of upper gastrointestinal endoscopy. The anaesthetic agent and oxygen 8 litres min^{-1} were delivered via a Bain anaesthetic circuit with a sevoflurane vaporizer (Sevotec 3, Ohmeda, Streeton, UK) and a nasal mask. The patient was familiarized with the mask and nasal breathing with oxygen alone, then sevoflurane was introduced at a concentration of 0.2% and increased by 0.2% every 30 s up to 1% and until a sedation score of 3 was achieved (induction time). The sedation score was adapted from Osborne and colleagues:[5] 1=fully awake; 2=drowsy; 3=eyes closed, but rousable to command; 4=eyes closed, but rousable to mild physical stimulation; 5=eyes closed and unrousable to mild physical stimulation. Heart rate and arterial oxygen saturation (Sp_{O_2}) were monitored continuously, and non-invasive arterial pressure, ventilatory frequency and sedation scores recorded every 2 min after the start of sedation. The time at which the patients first opened their eyes, sat up unaided and achieved discharge criteria (home-readiness) were recorded.

The endoscopist was asked to evaluate patient cooperation and ease of endoscopy during the procedure using a four-point scale. Before discharge from the day surgery endoscopy unit, patients were asked their opinion of the sedation and its effects, and also about recall of intraoperative events.

VAS scores were analysed relative to presedation levels using non-parametric Wilcoxon signed rank test for paired data. In all cases, $P<0.05$ was the criterion for statistical significance. The computer package used for all calculations was SPSS (version 6).

Thirty patients were recruited and completed the study. Mean age was 45.2 (range 27–68) yr, mean weight was 61.1 (range 40–92) kg and the male:female ratio was 17:13. Duration of induction was 7.8 (range 5–14) min and the duration of the procedure was 6.1 (range 3–14) min. Cardiovascular stability was maintained in all patients. All patients had an oxygen saturation of more than 98%. There were no airway obstructions or laryngospasms. No patient lost verbal contact during the sedation.

The endoscopist rated patient cooperation as excellent or good in 27 (90%) patients and fair in three (10%) patients. Ease of endoscopy was rated as excellent or good in 28 (93.3%) patients and fair in two (6.7%) patients. Overall patient acceptability was high. The majority of the patients (86.7%) said they felt relaxed and comfortable during the procedure. All but one patient stated they were willing to have the same type of sedation again. The patient who would not wish to have the same sedation again said that she felt uncomfortable and complained that she was awake throughout the procedure. She also had marked shivering at the start of sedation. Amnesia was observed in 19 patients (63.3%). However, only one patient had complete amnesia and 18 patients reported partial amnesia. Eleven patients did not have amnesia. One patient thought that the odour of sevoflurane was unpleasant. Sixteen patients (53.3%) found it to be slightly unpleasant. Five patients commented that the gas was pleasant while eight patients reported no smell. Two patients were disinhibited but this did not interfere with the endoscopy procedure. Two patients coughed slightly during the induction period. Dizziness occurred briefly in two patients after the operation. There was a significant reduction in anxiety scores, as assessed by VAS after sedation ($P<0.001$) (Table 1). Eye opening occurred in all patients immediately after the procedure.

Table 1. Anxiety score (median VAS score (quartiles)) and recovery profiles (min). *$P<0.001$, compared to pre-sedation score, Wilcoxon signed rank test

VAS scores	
Anxiety before sedation	5 (3–6)
Anxiety after sedation	0 (0–2)*
Time to	
Eyes opening	0.0 (0–0)
Sit up unaided	2.0 (2.00–3.25)
Home readiness	5.5 (3.75–10.00)

Our results indicate that inhalation sedation with sevoflurane is a satisfactory method for sedation during upper gastrointestinal endoscopy. Patient satisfaction was high and a significant number of patients were willing to have the technique again. Cardiovascular stability was good and respiratory depression or other airway difficulties did not occur. Speed of recovery is important for day case procedures. In this study, emergence from sevoflurane sedation was rapid and the patients were soon deemed to be home-ready (7.03 (SD 4.41) min). Similar findings were observed in a group of adult patients undergoing day surgery.[6]

Previous studies have shown that acceptance of upper gastrointestinal endoscopy is directly related to the degree of amnesia induced by the sedation.[7] However, despite a low incidence of complete amnesia, we found that not only was patient acceptance high but the majority of patients felt relaxed and comfortable during the procedure. Whether amnesia is needed for tolerance has been disputed.[8]

To successfully use inhalation sedation, the odour of the gas is an important factor. In this study, only one patient found breathing sevoflurane unpleasant. The majority of the patients (53.3%) found sevoflurane to be slightly unpleasant but tolerated the induction quite well. Laryngospasm or breath holding were not observed while coughing occurred in two subjects; this was 'mild' and did not adversely affect oxygen saturation. Thus odour is not a problem with 1% sevoflurane in 100% oxygen. This is in agreement with other reports.[9]

In conclusion, we showed that sevoflurane–oxygen inhalation may provide a valuable alternative to a conventional sedation regimen for adult day-case patients undergoing diagnostic upper gastrointestinal endoscopy. Further randomized controlled studies are required to compare sevoflurane–oxygen sedation with other conventional sedation regimens.

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Book Reviews

Handbook of Headache. R.W. Evans and N.T. Mathew. Published by Lippincott Williams and Wilkins, Philadelphia. Pp. 339; indexed; illustrated. Price £25.00. ISBN 0-7817-18775.

Headache can be a nightmare symptom for clinicians. It is one of the commonest presenting symptoms in primary care and is usually benign, but it may occasionally herald a sinister and life-threatening condition. For those who are not headache specialists, a book which will help them steer a course between over-investigation and missing important pathology is most welcome. Most anaesthetists working in pain management fall decisively into this category, and they will find the *Handbook of Headache* a very useful addition to their bookshelves.

The first thing to say about this book is that the word 'handbook' is only appropriate in terms of its physical size. Within a pocket-sized format is packed a fully-fledged textbook of headache with nearly 500 references. It is, however, well-written, informative and extremely readable. The book begins with a clear account of the diagnosis of headache and then goes on to review the field in a series of chapters which are varyingly presented in terms of diagnosis and presentation. At first, it seemed a little inconsistent to switch from 'Cluster Headache' to 'First or Worst Headache', but it is a reasonable reflection of the thought processes involved in assessing this symptom and achieves overall clarity. The self-test material at the end is excellent, although perhaps a little weighted in favour of sinister diagnoses that are easy to miss. The section on post-lumbar puncture headache was particularly cheering for anybody from an anaesthetic background to read in a textbook written by neurologists. It is to be hoped that this chapter will be widely read and digested by all those UK physicians and radiologists who still use bevelled needles for lumbar puncture.

One criticism of this book, from the perspective of a specialist in chronic pain, is that it lacks a biopsychosocial perspective. The majority of headaches fall within the umbrella of a chronic pain syndrome, but there is no overt recognition of pain as a sensory and emotional experience and where psychological or psychiatric input is recommended there is a feel that it is for patients whose pain is 'non-organic'. This is rather old-fashioned and, in practice, many people with headache may benefit from a multidisciplinary approach to their management. In similar vein, the section on complementary therapies was so scant as to be almost dismissive. In the UK many pain management units use acupuncture in the management of headache, especially migraine, and I felt it warranted more than the brief account of the Chinese model found here. Another criticism is that the book was not revised for the UK market. In the discussion of analgesic headache (an important topic) butalbital, a barbiturate not used in the UK, is listed as one of the commonest drugs implicated. Caffeine is a culprit common to both cultures, but what should have been a useful list of the caffeine contents of a range of foods, beverages and over-the-counter medicines remains purely American. There are other examples dotted throughout the book, but none of these criticisms detract from the fact that this is an informative resource to which I expect to return frequently.

In summary, this is an excellent and readable review of headache which will be extremely useful, not only to chronic pain consultants and other non-neurologists in secondary care who have to deal with this complaint, but also to general practitioners who actually manage the overwhelming majority of patients with this common symptom.

J. Jessop

Cardiovascular Drugs in the Perioperative Period P. Fox, G.G. Harrison and L.H. Opie (editors). Published by Lippincott Williams and Wilkins, Philadelphia. Pp. 391; indexed; illustrated Price US$52.95. ISBN 0-620-23099-1.

The editors set out clearly the importance of their subject matter in the preface. The prevalence of drug treatment for cardiovascular disease in the surgical patient population makes a knowledge of the contents of the first six chapters on the pharmacology of cardiovascular drugs in perioperative use essential reading for all anaesthetists. The latter six chapters are gathered under the title 'drug management of disease and disaster in the perioperative period'. They apply the information provided earlier to clinical conditions and adverse events likely to be encountered during anaesthesia. Four principal aspects of cardiology; arrhythmias, hypertension, ischaemic heart disease, and heart failure receive a chapter each. The last two chapters summarize cardiovascular drug treatment during resuscitation and intensive care, and cardiopulmonary bypass.

The pharmacology section begins with a description of the autonomic nervous system in order to characterize the sites of action of cardiovascular drugs. The effects of anaesthetic agents on the heart and circulation follow, then there are chapters on adrenergic agonists, inhibitors, drugs affecting calcium channels and vasodilators. Choosing to make each chapter complete in itself, the editors have accepted a fair amount of repetition. For example, the chapters on adrenergic receptor agonists and adrenergic inhibitors both contain descriptions and diagrams of an adrenoceptor. Although Opie's diagrams are redrawn quite differently, the accompanying descriptions differ less. The resuscitation chapter contains flow charts from both North American and European practice to guide treatment. The chapter on vasoactive drugs and cardiopulmonary bypass gives a brief summary of much of the preceding book. Throughout the book, the writing styles are consistent, despite chapters originating from North America, South Africa and Europe.

Intended as a handbook for use in the operating theatre, the intensive care unit and the ward, this book has the unusual dimensions of 12 × 25 × 2 cm, making it just short of A4 size in height and a little over half the width. For any anaesthetist still wearing a white coat, the handbook would fill a side pocket. It could not be contained by operating theatre clothes. The wealth of information makes this volume a weighty tome. Tipping the scales at half a kilogram it would distort the cut of a jacket. The page layout is very convenient and the text is punctuated by useful and clear line diagrams. However, the font is journal size rather than textbook size and chapters of 60 pages can take some time to digest.

The text is concise and yet far more detailed than required for the FRCA primary examination. It is not a book to read in a comfy chair with music playing. Time would be spent better at a well lit desk with some minutes free from distraction. Like seeing a film before reading the original novel, some prior knowledge of the subject will help navigation through this text. The resuscitation chapter has algorithms for clinical management, but apart from this, the book is not a cookbook for immediate treatment. However, if used in the manner intended, as a handbook for regular reference close to the clinical environment, the reader will be well rewarded with a good understanding of contemporary clinical pharmacology of cardiovascular drugs and how their use can be related to clinical practice.

D J R. Duthie

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Problems in Anesthesia: Frontiers in Anesthesia, Vol. 12, No. 1, 2000. L.A. Fleisher and D.S. Prough (editors). Published by Lippincott Williams and Wilkins, Philadelphia. Pp. 109; indexed; illustrated. Price US$56.00. ISSN 0889-4698.

This book, 109 pages long, consists of 13 chapters by 17 contributors. It attempts to address a selection of issues under the heading of *Frontiers in Anesthesia*. Four of the chapters focus on a clinical topic. Six of the chapters have a medico-political theme Of these, three chapters deal with the future of anaesthesia, one looking at lessons from the past, one with an organizational perspective, and one with a business perspective; and three chapters debate the role of the anaesthetist as a perioperative physician, with contributions arguing both for and against, alongside a European view The remaining three contributions deal with the Internet, anaesthesia in developing countries, and risk in anaesthesia outside the hospital. There is an index of three pages.

All but three of the contributors work in the USA, and this brings a distinct perspective to those chapters which deal with organizational matters. There is, for example, a whole page devoted to the ASA strategic plan, and a detailed historical review of the anaesthesia workforce and NIH funding. That is not to say that the American view is devoid of interest in Britain. The chapter on anaesthetic risk outside the hospital environment is fascinating; its account of office surgery in New York offers a sobering contrast to recent approaches to the management of risk in community dental anaesthesia in the United Kingdom.

The choice of clinical subjects for review is crucial to a compendium like this. These include cardiovascular outcome studies, α_2-adrenoreceptor agonists, monitoring of anaesthetic effect and blood substitutes. All four are topical, and it is likely that they will remain so for the foreseeable future. The chapter on cardiovascular risks, by Mangano, concentrates heavily on the author's work on the effect of atenolol in reducing postoperative cardiovascular mortality. This landmark work is described in no fewer than seven pages, and the chapter concludes with guidelines on perioperative use of β-blockers. The chapter on α_2-agonists is a systematic and balanced account of the basic pharmacology and clinical use of these agents. After reviewing the difficulties intrinsic to monitoring depth of sedation and anaesthesia, the chapter on monitoring of anaesthetic effect concentrates on bispectral index There is an interesting emphasis on avoiding excessively deep anaesthesia, and the cost savings which may be obtained by titrating anaesthetic depth to a bispectral index; avoidance of awareness takes second place. The final clinical contribution, on blood substitutes, offers a good account of the risks of transfusion and the physiology of oxygen transport, both perfluorochemicals and haemoglobin solutions are reviewed.

Perhaps the most challenging chapter is entitled 'Anesthesiology in the New Century: A Business Perspective'. Beginning with the assertion that health care is big business, worth more than $1 trillion per year in the USA, there follows a perspicacious look at the future of drug development and clinical trials in our specialty.

The contributions are all relatively short; all are readable and none is without interest. The question remains in this reviewer's mind as to whether the whole is more than the sum of the parts. I enjoyed reading all of the chapters, but I am left with a series of snapshots rather than a unified totality. At the price, this book will probably remain the preserve of the library rather than the individual reader. The individual clinician will get better value for money from a comprehensive textbook.

C. J. R. Parker

ABC of Intensive Care. M. Singer and I. Grant (editors). Published by BMJ Books, London. Pp. 52; indexed; illustrated. Price £15.95. ISBN 0-7279-1436-7.

In recent years, BMJ Books have published a wide range of high quality ABC books and *ABC of Intensive Care* continues with this tradition. Mervyn Singer and Ian Grant have invited an impressive range of high profile intensivists from throughout the United Kingdom, as well as representatives from nursing, physiotherapy and audit research to contribute to this book. Despite the multiple authorship nature of this short 52-page text, the result is a concise and consistently coherent overview of intensive care practice in this country. Each chapter attempts to cover as much ground as possible using limited text. Diagrams and photographs are used with extremely good effect. Provided you realize that this book is about breadth and not depth, it makes an impressive read.

Appropriately, the first chapter details how an ITU is organized and structured. The photographs presented in this chapter are worthy of note in that they make for an interesting historical comparison of old with modern ITU practice. This is followed by a chapter that addresses the difficulties involved in deciding on the appropriateness of ITU admission. Approximately half of the remainder of the book is devoted to a conventional discussion of organ failure and its management, whereas the last chapters focus on less appreciated but equally important topics.

'Organ dysfunction' clarifies the link between infection (and other insults), inflammation and organ failure, and the vital role of cellular hypoxia is emphasized. The next four chapters described specific organ system failure and modern approaches to management. In common with all sections of this book, the chapter on respiratory support is completely up-to-date and describes the increasing popularity of non-invasive ventilation, prone positioning and lung protective ventilation strategies in acute respiratory distress syndrome. The next chapter on circulatory support is equally informative in mentioning the recent controversy over the use of the pulmonary artery flotation catheter and the contentious area of preoperative optimization of the high risk surgical patient. I liked the authors' inclusion of simple clinical criteria when assessing tissue perfusion to remind us that intensivists are doctors rather than applied physiologists. The diagrams in this chapter were particularly impressive. The chapters on renal and neurological support continued the set pattern and again offered an informative synopsis on managing these problems.

Although all of the aforementioned chapters are well written and valuable, the reason I enjoyed reading this book was the inclusion of the remaining chapters which detail areas of intensive care medicine which are often omitted from conventional texts. 'Other supportive care' covers physiotherapy, mobilization, and skin care. These areas are often delegated to non-medical staff and are under-appreciated by intensivists. Psychological support was also covered, another important area often delegated to nursing staff. I was pleased to find a chapter devoted to withdrawal of treatment and was impressed by the commonsense approach to dealing with problems which may arise when patients' families and referring clinicians have a different view to that of the ITU team. I was equally impressed to find a chapter focusing on what happens to ITU patients following discharge and how the ITU team can enhance quality of care during rehabilitation The book ends with a comprehensive but unavoidably superficial description of cutting edge technology in ITU medicine, the value of which will be decided by time.

This book does not pretend to be anything but an up-to-date and necessarily brief summary of ITU practice in the United Kingdom. Nevertheless it does its job very well and is all the more impressive for including some under-appreciated topics in ITU medicine. At £15.95 it represents good value for trainees exposed to ITU for the first time; other specialists with a peripheral involvement in ITU; medical students; and nursing and other paramedical staff with ITU responsibilities. This book was not really written for experienced ITU clinicians but still deserves a place on the library shelf in every ITU department.

G. R. Masterson

The Evolution of the Anesthesia Machine, on CD-ROM. R. Ortega and H. Arkoff in collaboration with the Wood Library Museum.

This educational material was conceived, created and published by the authors, both of whom are full time practising anaesthesiologists at Boston University Medical Center, without the assistance of a commercial publishing house. The authors carried out all the computer programming. Almost all photographs and video segments are the original work of the authors.

The work is based on the Wood Library Museum (WLM) collection of material and equipment relating to the history of anaesthesia and won first prize in the Scientific Exhibition of the 1998 ASA Annual Meeting. It contains only limited mention of the development of European anaesthesia machines.

The disc is not for sale but is provided and distributed free of charge. The authors emphasize that corporate sponsorship is being used solely for this free provision.

The original plan was to publish this material as a DVD, which has a much higher capacity than a CD. Owing to delays in the widespread use of this technology, the authors have issued an abridged version in CD format. The chief result of this is seen in the interviews section (see below) where, in most cases, the 'talking head' is lost but the important sound is retained. (The preceding three paragraphs are a lightly edited version of the authors' letter accompanying the disc.)

The contents of the disc are divided into five sections the first being an introduction delivered by Dr Elliot Miller from the Ether Dome at the Massachusetts General Hospital. The second section is entitled 1846; selection from a grid of sixteen squares gives a comprehensive survey of the events and personalities of that momentous year. Inhalational anaesthesia began in New England and it is appropriate that as well as coverage of Morton, Crawford Long, Horace Wells and others we should also see tombs, monuments and memorials related to these pioneers. The items on the Ether Dome show how thoroughly this National Monument has been restored.

The third section is Timelines; a year by year survey of the development of inhalational anaesthesia. The material here is mostly American but Davy, Snow and Clover do receive honourable mention as do Hewitt (foot controlled N_2O) and Vernon Harcourt. A large number of machines of various sorts are shown and there is a tendency to show a variety of cylinder yokes manufactured in the Mid West. These must represent a strength of the WLM collection. Under the year 1980 are shown Robert Macintosh's FRCS robes and under 1991 a bust of Pepper Jenkins. The biggest defect of this section is a failure to explain how any of the well illustrated equipment works. No diagram of any kind is provided.

The next section is entitled Interviews. Twenty-four American anaesthesiologists answer written questions which it is clear they have set themselves. Most of the participants in this section are trustees of the WLM and have many reminiscences of olden times. Professor Eger ventures that, despite its drawbacks, nitrous oxide will be with us for the foreseeable future. Robert Tham, an engineer working for Ohmeda considers that low flow is the trend of the future. Nicholas Greene, who has edited both American journals, observes that after early enthusiasm, writing on anaesthetic equipment in American journals has restricted itself largely to letters but British journals have, over the years, produced a series of important papers on breathing systems. George Bause, the Hon Curator of the WLM (who has Humphrey Davy as a 'distant uncle') is interesting on WLM exhibits which include a number of English vaporizers. He identifies a Great Lakes school of anaesthetic equipment design and manufacture based on Cleveland, Toledo, Chicago and Minneapolis. Dr Bause also notes the strong bias of the WLM towards Ohio–Ohmeda. For reasons largely historical Draeger, now the other major world manufacturer, is almost excluded. Also described are exhibits of American anaesthetic equipment in the two world wars. The original Boyle machine was a copy of the Gwathmey, engineered to take British cylinders. It did eventually take on an identity of its own with the Boyle's bottles, the Magill attachment and better flowmeters.

The final interview is with Dr Lucien Morris who describes how his work on chloroform with Ralph Waters focused attention on the need for accurate vapourizers. The design of the copper kettle arose from the Pinson 'bomb' and the Oxford vapourizer No. 2 to which the disc of sintered material was added to break up the gas stream and facilitate vaporization.

The final short section on the disc is a disappointment, it is entitled The Future. The possibility of manufacturers of anaesthetic equipment being automatically notified of any malfunction of their equipment is raised. It is of interest to hear the inventor of BIS speaking against closing the loop (controlling the anaesthetic machine by a measurement of depth of anaesthesia).

This disc is of very uneven quality. The first part, 1846 and Timelines is good; the second part, Interviews and The Future, is not. There are bad spelling mistakes, many affecting people's names. Speech is sometimes cut short and the content of some of the interviews is slight. Those who are interested in the history of anaesthesia will appreciate the first part of this disc. The Wood Library–Museum of Anesthesiology is explored; it is located in Park Ridge, Illinois, near Chicago.

D. C. White

Location and Cannulation of Central Veins using Ultrasound, on video. Published by Leeds University Television, Leeds. Price £25.00

For many years I took great pride in my ability to successfully cannulate central veins, especially when others had failed but, of course, I conveniently forgot the morbidity sometimes caused by my persistent endeavours. Then a few years ago I watched a radiologist, using ultrasound guidance, deftly cannulate a central vein which I had failed miserably to locate. I suddenly realized just how crude our blind techniques were and became totally converted to the location and cannulation of central veins by ultrasound. I remain surprised how few of my colleagues have undergone a similar conversion and suggest that those who consider it rather 'unmacho' to use ultrasound vision simply have not yet seen enough serious morbidity associated with their blind stabbings. They will!

Hopefully, this video will help disseminate the value of this important new method and it is only fitting that it comes from the anaesthetic department at Leeds General Infirmary, which has already done much to promote its use in the anaesthetic literature.

Although only 13 minutes in length, it clearly demonstrates all the important aspects of the technique including the ultrasound anatomy of the internal jugular, subclavian and femoral veins, cross-sectional and longitudinal views of needle insertion and, very importantly, the method of rendering the ultrasound probe sterile. Correctly, emphasis is on cannulation of the internal jugular and femoral veins since ultrasound is less helpful with that to the subclavian vein. The apposition of the anterior vein wall to the posterior wall by the cannulating needle and its penetration of both is well demonstrated, readily explaining why blood is often aspirated only on needle withdrawal.

One of three videos from the Leeds group (the others are about percutaneous tracheostomy and haemodynamic monitoring) this is the most important because whereas few would question the clinical value of the other two, the use of ultrasound for central vein cannulation remains relatively novel. Put a portable ultrasound monitor top of next year's medical equipment requisition list and justify the £4500 expenditure by quoting the last sentence of an excellent editorial by D.H.T. Scott which appeared in this journal last year: 'We have not yet reached the point where it is considered by our legal colleagues to be negligent to attempt to insert a central venous cannula without checking the anatomy by ultrasound, but early in the next Millennium, I am confident that ultrasound guidance will be a pre-requisite before and during central venous cannulation'.[1] Also ask the manufacturers to provide a free copy of this excellent video with their monitor.

R.G. Wilkes

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1 Scott DHT. 'In the country of the blind the one-eyed man is king', Erasmus (1466–1536). *Br J Anaesth* 1999; **82**: 820–1

Vascular Access Procedures and Haemodynamic Monitoring, on video. Published by Leeds University Television, Leeds. Price £28.00.

Both anaesthetic assistant and trainee anaesthetist are required to learn a barrage of new skills and techniques from an early stage in their training. Both must rapidly master the preparation and insertion techniques for vascular access and haemodynamic monitoring. This short, 15 min, video takes the trainee through setting up a pressure monitoring transducer; the insertion of an arterial line; central venous cannulation; and finally the correct positioning of a pulmonary artery catheter through an introducer.

First, a standard pressure transducer is run through with heparinized saline, flushed and finally zeroed. An arterial line is inserted into the radial artery using local anaesthetic in an awake patient. The vessel is successfully cannulated using a standard Seldinger technique. The latter is connected to the pre-prepared transducer and an arterial trace displayed on the monitor. The video and commentary move on to the slightly more involved insertion of a triple lumen central venous catheter into the right internal jugular vein of the now anaesthetized patient. The standard technique of skin preparation and towelling is employed, once the patient has been placed in the head down position. Explanation of anatomical landmarks is given and the catheter is inserted with consummate ease by the expert operator.

Surprisingly, a second cannulation of the right internal jugular vein is carried out with the insertion of a pulmonary artery catheter introducer, adjacent to the first central venous line. The pulmonary artery catheter is passed through the introducer having first been flushed and prepared with three-way taps, and the pressure transducer is attached to the distal lumen. The video finishes by visually and verbally describing the pressure waveforms produced as the catheter passes from the internal jugular vein to the pulmonary artery.

This video was produced by the University of Leeds for the Academic Unit of Anaesthesia based at Leeds General Infirmary. As a training video it will assist both the junior anaesthetist and theatre technician, giving an overview of the techniques described. Camera work is clear, sound realistic and commentary both relevant and informative. The film is short and extremely concise Only the most essential explanation of procedures is given. Indeed no explanation is provided as to what 'zeroing the pressure transducer' refers to or why the head down position is employed during central venous cannulation. One cannot help but feel that a supplementary and more detailed video of each technique would be useful, this compilation serving to provide an overview of the techniques illustrated. In this role, however, this video is a competent and valuable addition to any anaesthetic training programme.

J. Scott

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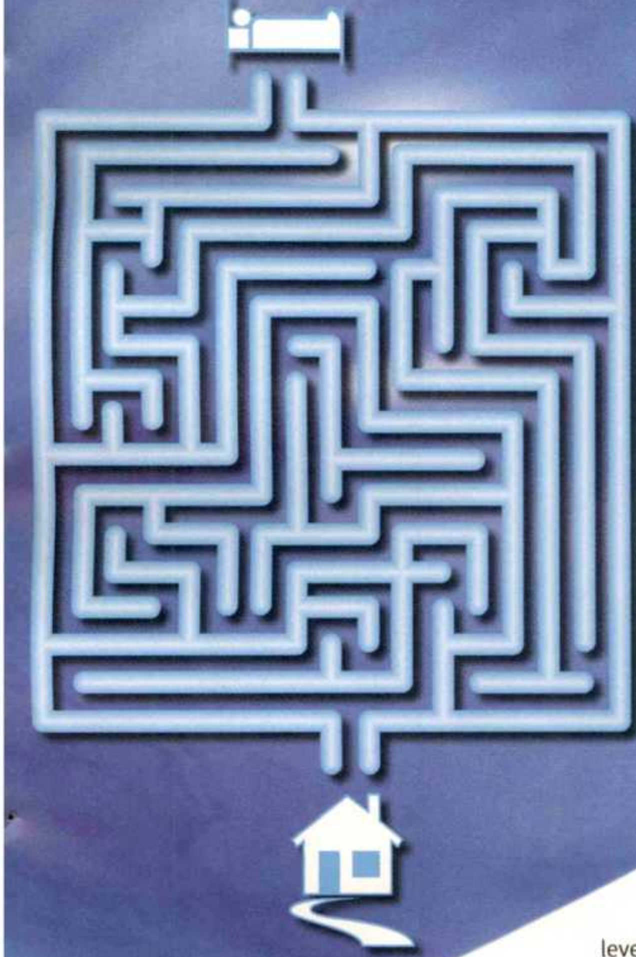

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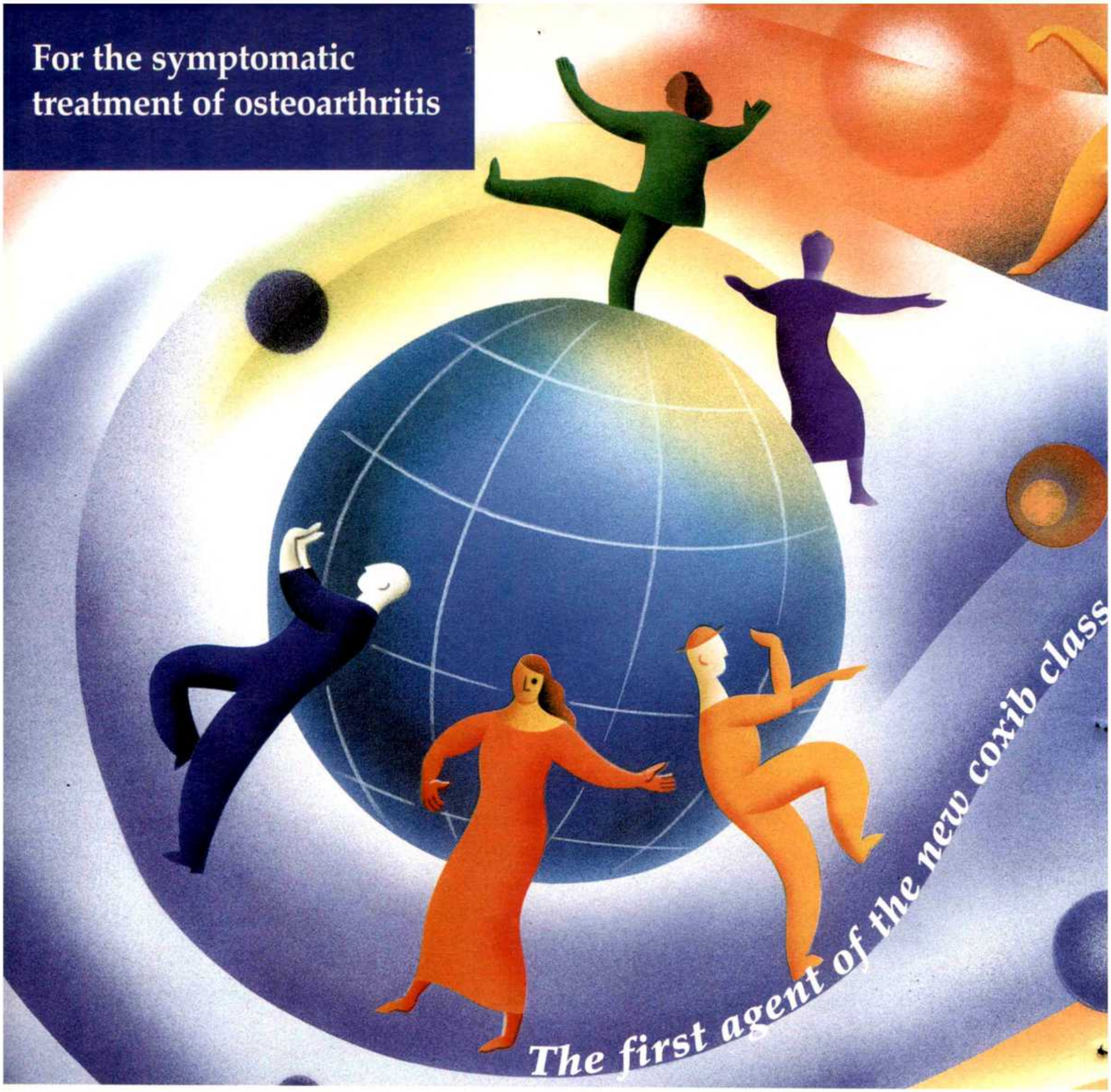
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(rofecoxib)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib.

VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.

Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of

In clinical studies: inhibits COX-2 but not COX-1[1]*

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*** statistically significant inhibition of COX-1 has not been documented with any dose of VIOXX given to humans.**

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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58.

Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers

Tablet 12.5 mg	PL 0025/0383
Tablet 25 mg	PL 0025/0384
Oral Suspension 12.5 mg/5 ml	PL 0025/0385
Oral Suspension 25 mg/5 ml	PL 0025/0386

Marketing Authorisation holder

Merck Sharp & Dohme Limited
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POM **Date of review:** May 2000.

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References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastro-intestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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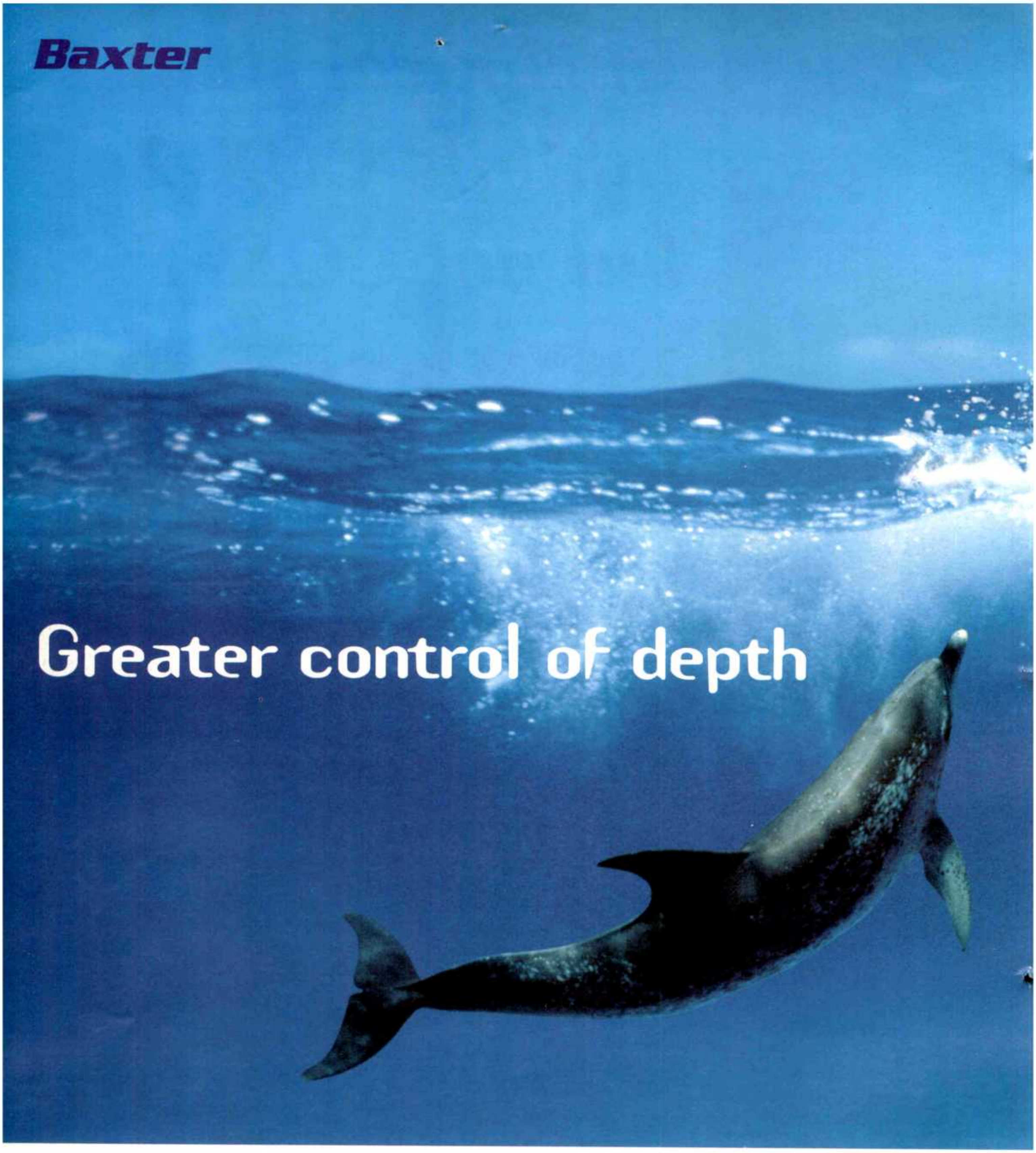
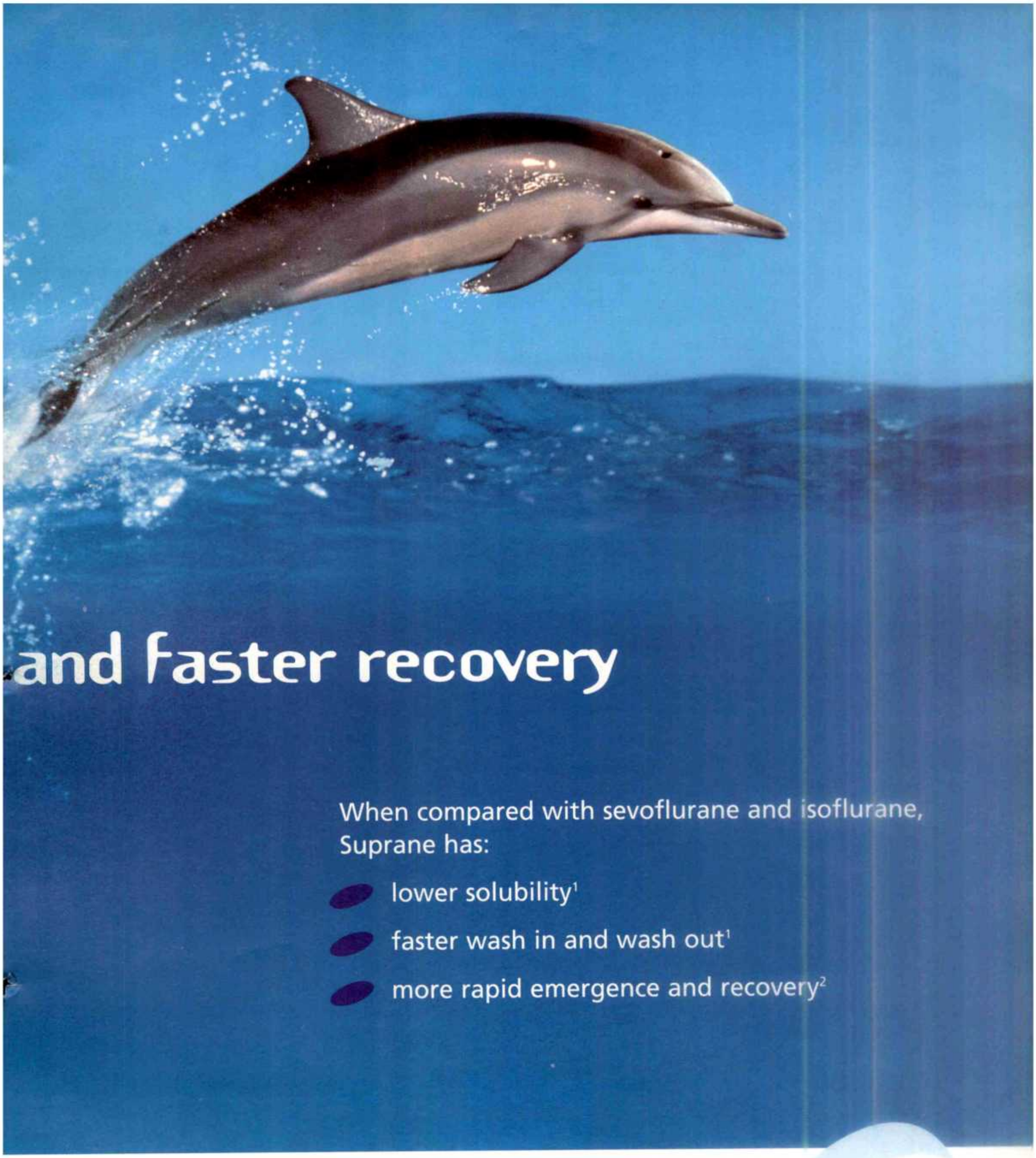


SUPRANE® (desflurane) PRESCRIBING INFORMATION
Presentation: Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast



When compared with sevoflurane and isoflurane, Suprane has:

- lower solubility[1]
- faster wash in and wash out[1]
- more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

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References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

Suprane® desflurane

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SUP021/UK/0200

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Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

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References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

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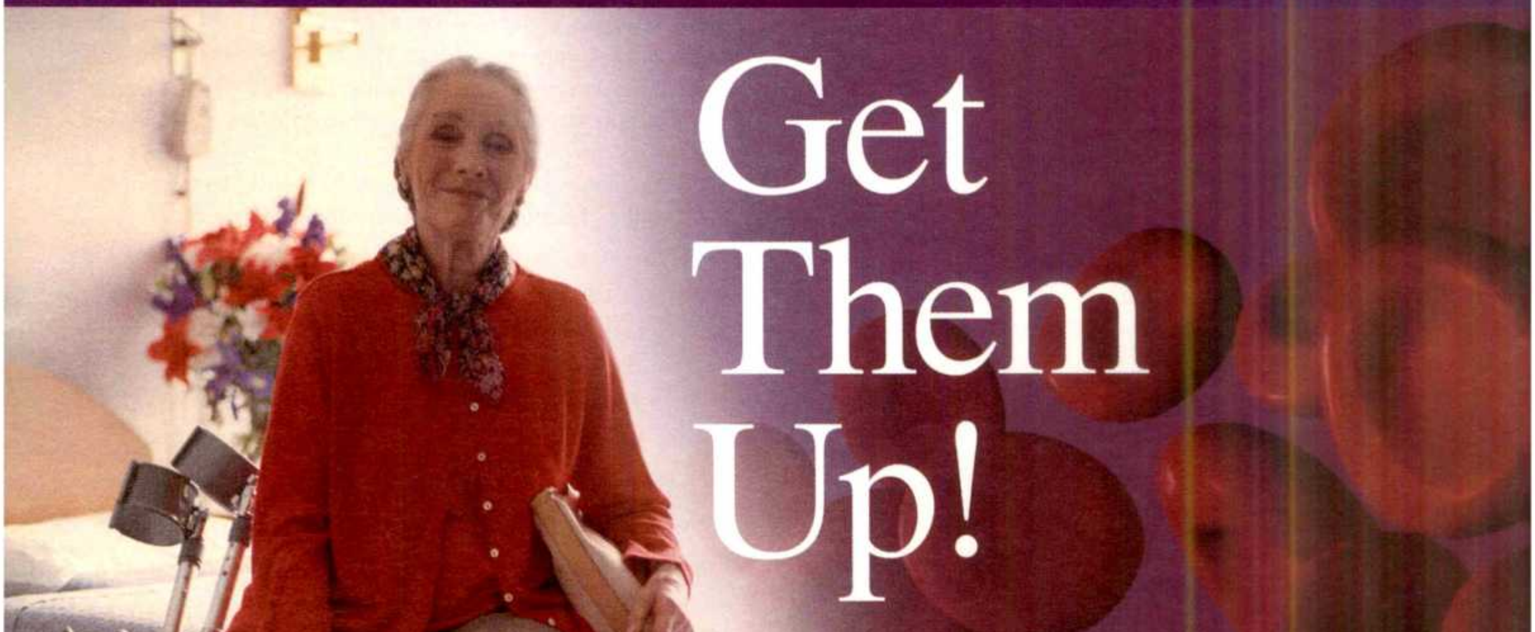

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Editorial Notices

Royal Medical Benevolent Fund

The Royal Medical Benevolent Fund reminds readers of its Christmas Appeal. Your generosity last Christmas enabled the Fund to distribute additional seasonal support of £75 000 to help bring some semblance of happiness and dignity to those doctors, and particularly their bereaved families, less fortunate than us. Each year our general grants total over £800 000. The fund always seeks to give this extra help at Christmas with gifts to the children involved.

Contributions marked 'Christmas Appeal' may be sent to the Chief Executive Officer of the RMBF at 24 King's Road, Wimbledon, London SW19 8QN or to the Treasurer of your local guild of this Fund. (Cheques payable to RMB Fund.)

BJA/RCA Research Grants

The *British Journal of Anaesthesia*, in conjunction with the *Royal College of Anaesthetists* is making a further round of grants available to support research in anaesthesia, intensive care or pain relief. The work must be conducted in the United Kingdom.

Grants are available to support specific projects in anaesthetic departments. Joint applications with basic science departments will be welcome. These grants may be awarded to fund technical staff, research students or post-doctoral research fellows: salaries, or items of equipment. The maximum value of any award will be £50 000, and the *BJA/RCA* will not contribute towards overheads.

The *BJA/RCA* will not be funding Research Fellowships with this round of awards. Applicants should note that candidates will usually be established members of academic departments of Anaesthesia in the United Kingdom; and the grant must be administered by an academic department of Anaesthesia and have the support of the Head of that Department.

For further details and forms, please **WRITE** or **e-mail** to:

Dr J. W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Headington, OXFORD OX3 9DU *or*
john.sear@nda.ox.ac.uk

Closing date for applications is **January 19th 2001**. Late applications will **not** be considered.

Resuscitation Fluids: Update 2000

Institute of Electrical Engineers, London, UK, November 17, 2000

Organised by the Centre for Anaesthesia, Royal Free and University College Medical School (RFUCMS), London, UK and The National Hospital, University of Oslo, Norway. This meeting has an internationally renowned faculty who will be cross examined by a panel of experts on topics including: Is albumin dead? Haemoglobin: How low can you go? Abnormal saline; The ideal colloid; Hyperoncotic/hyperosmolar; Risks of blood transfusion – oxygen carrying solutions.

Immediately following the meeting there will be a twilight trip to the 'London Eye' for all interested parties.

For further details please contact: Dr Monty Mythen, Centre for Anaesthesia RFUCMS, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London W1N 8AA, UK.

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St Bartholomew's Hospital Choral Society

Royal Albert Hall, London, UK, November 21, 2000

St Bartholomew's Hospital Choral Society celebrates the millennium and their 35th anniversary with the Royal Medical Benevolent Fund as their chosen Charity for their season 2000/2001.

Mahler's Symphony No. 8 'Symphony of a Thousand' with the Royal Philharmonic Orchestra, Royal Albert Hall, 21 November 2000.

It needs a *really* big choir, splendid orchestra, fine soloists and conductor. Six hundred singers are needed for this monumental work.

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Tel: +44 1628 664157.

Or to support, details available from:

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Tel: +44 20 8540 9194; Fax: +44 20 8542 0494;
E-mail: rm.bf@virgin.net

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
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Deadline for abstracts: December 10, 2000.

For further information contact us via e-mail at mac@mskcc.org or visit our web site www.maacc.org or by mail: Ruth Reinsel, PhD, Dept of Anesthesiology/CCM, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10021, USA.

Tel: +1 212 639 6038; Fax: +1 212 772 8646.

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

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For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

Association of Cardiothoracic Anaesthetists

Symposium on Cardiopulmonary Transplantation
Newcastle upon Tyne, UK, February 1, 2001

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For further information and registration details please contact: Dr S. R. Haynes, Department of Cardiothoracic Anaesthesia, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN, UK.

Tel: +44 (0) 191 2843111, ext: 26488; Fax: +44 (0) 191 2231175; E-mail: judith.iley@nuth.northy.nhs.uk

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)
Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

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16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

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Third European Congress of Orthopaedic Anaesthesia 2001

Royal Lancaster Hotel, London, England, May 31–June 2, 2001

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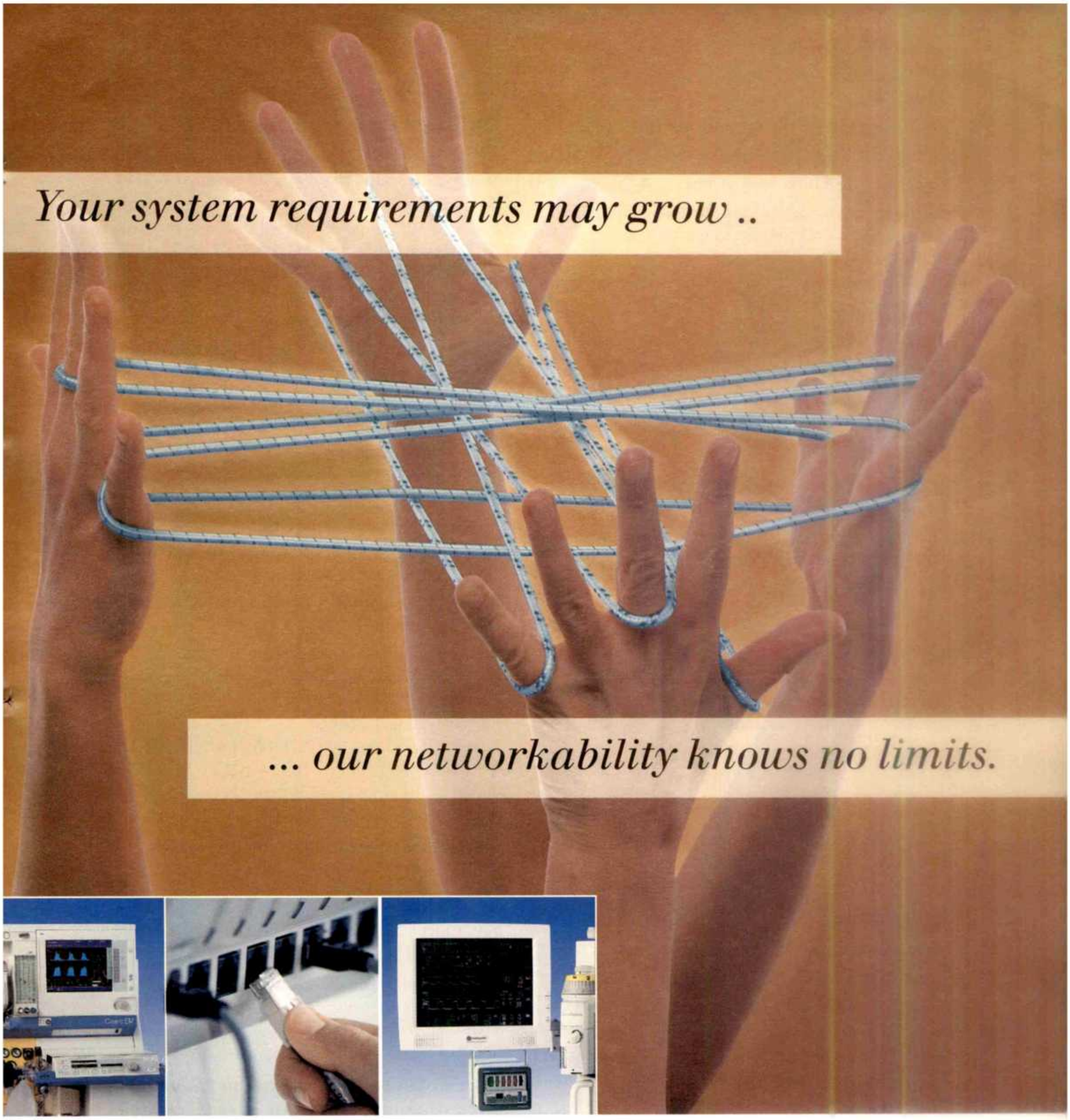
German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001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26th Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Tromsø, Norway, June 13–17, 2001

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Web site: www.ssai2001.org

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

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ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

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Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:
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First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

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8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:
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German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:
Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.
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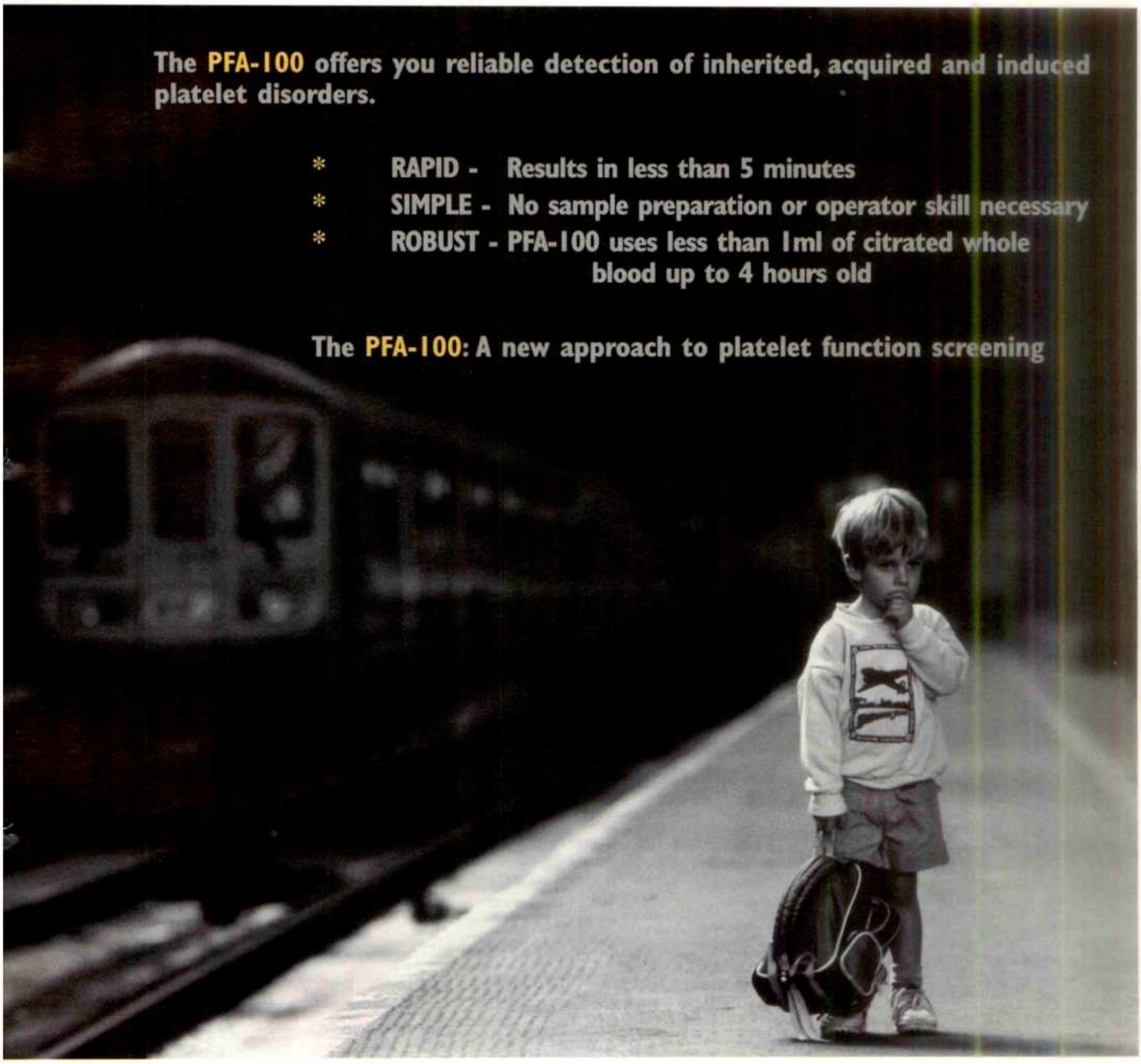

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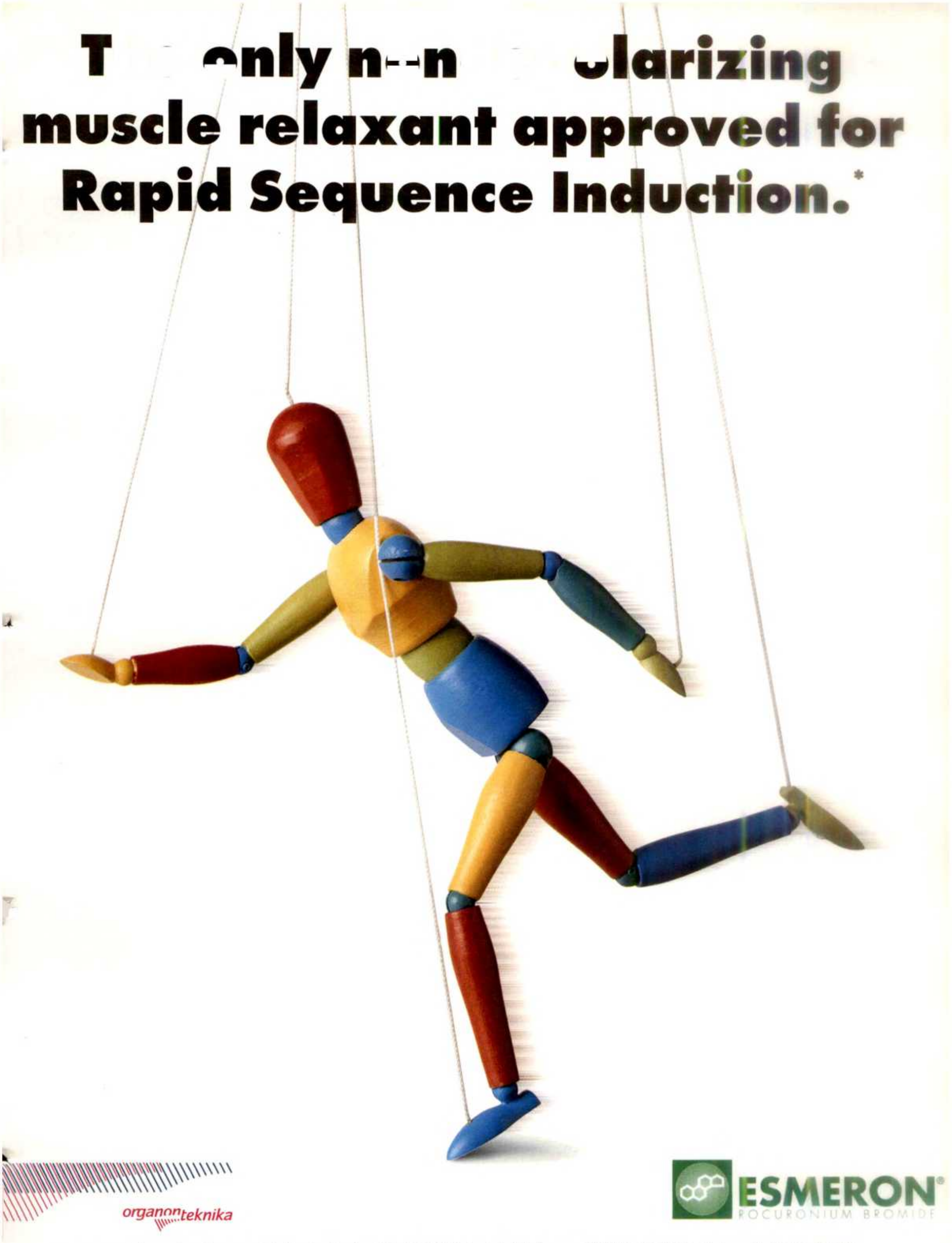
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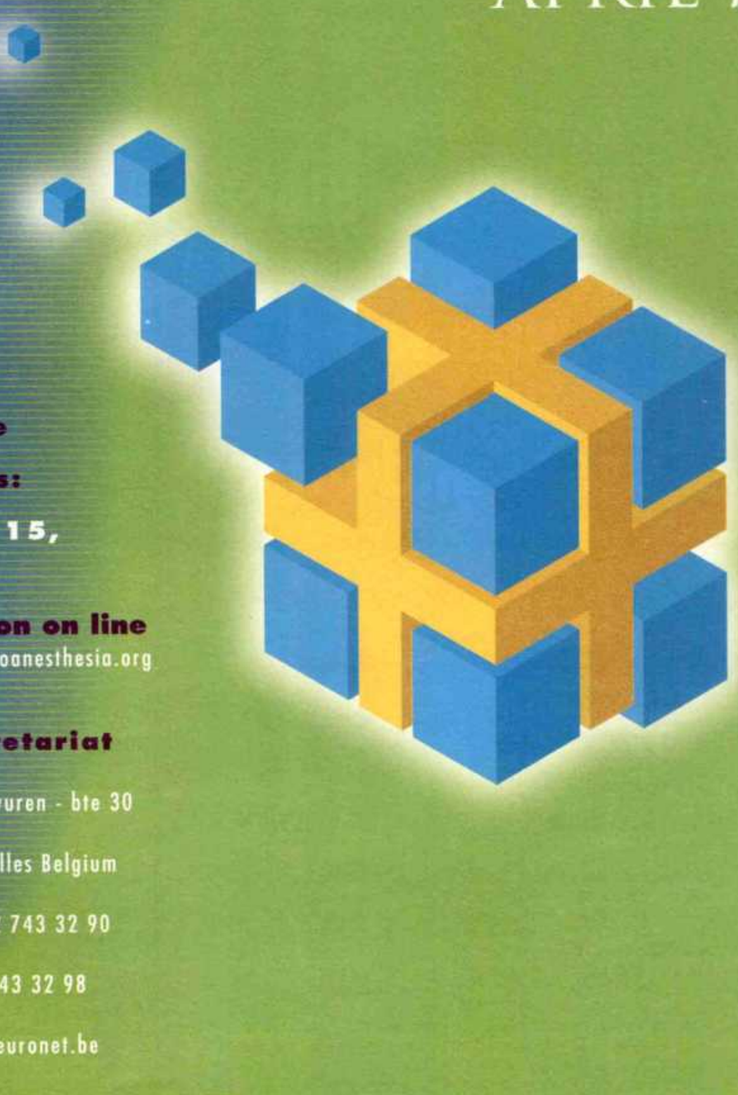

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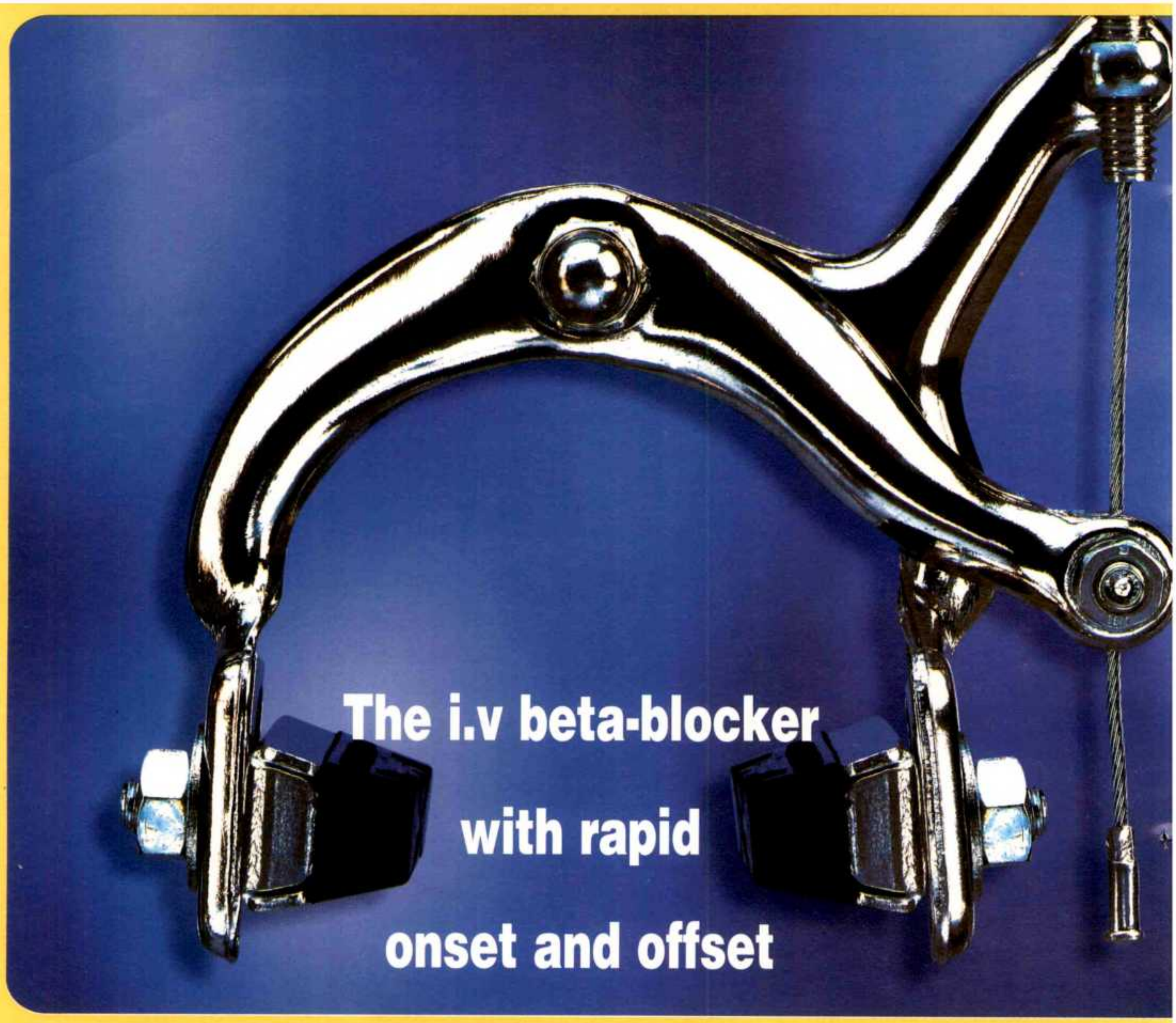

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BRITISH JOURNAL OF ANAESTHESIA

Volume 85, Number 5, November 2000

Editorial

Postoperative nausea and vomiting—time for balanced antiemesis?

The last decade has seen considerable advances in the management and prevention of complications occurring after anaesthesia and surgery, especially of acute pain. Can the same be said for postoperative nausea and vomiting (PONV)? There is no doubt that a vast amount of research has been published in this area and new classes of antiemetics have been introduced. However, although data are not available to compare precisely the present incidence of PONV with that 10–15 yr ago, there is a general impression that there has been little progress.[1]

The 1990s was the decade of the 5-HT_3 receptor antagonist. Their effectiveness in the prevention of chemotherapy-induced nausea and vomiting was very impressive[2] and this begot great expectations with respect to potential efficacy for PONV. Ondansetron, and to a lesser extent other 5-HT_3 antagonists, have now been evaluated extensively. Although they are very effective compared with placebo and have relatively favourable side-effect profiles, their absolute efficacy is disappointing. For example, in a systematic review of ondansetron for the prevention of PONV, the best numbers-needed-to-treat for the prevention of PONV was 5–6.[3] Most consider droperidol as an effective antiemetic but it is associated with side-effects such as agitation, sedation and extrapyramidal reactions.[4] Its efficacy has been compared with ondansetron by several investigators and a recent meta-analysis suggested a similar efficacy for droperidol and ondansetron, although ondansetron may be superior in children.[5] This study also confirmed the conclusions of others[4 6] that metoclopramide is relatively ineffective for the prevention of PONV.

Antagonists at the NK_1 receptor represent another new class of antiemetics. Emetic inputs converge in the brainstem in areas where the NK_1 receptor is in abundance and animal studies indicate that NK_1 receptor antagonists have a wide spectrum of antiemetic activity.[7 8] There are some data suggesting efficacy in humans after chemotherapy[9] but there is a paucity of published information with respect to prevention of PONV. However, in a study investigating the treatment of patients with established PONV, 44% required rescue antiemesis during a 6-h period after administration of an NK_1 antagonist (GR205171) compared with 67% after placebo.[10] These early data suggest that NK_1 antagonists have antiemetic properties and may be useful agents but it seems unlikely that they will be the final solution for PONV.

Dexamethasone has now emerged as potentially useful prophylaxis for PONV. Its efficacy is comparable with other antiemetics but it may be more effective in the prevention of late PONV with a numbers-needed-to-treat of 4.3.[11] Cannabinoids have antiemetic properties[12] and these drugs may be available for medical use in the future. We can only speculate at present as to the effect of cannabis or any of its constituents on PONV. However, there was no difference between the effect of nabilone and metoclopramide in patients after hysterectomy.[13]

Non-pharmacological methods can be effective. Traditional and laser stimulation acupuncture[14 15] and acupressure[16] have been shown to be more effective than placebo. Their efficacy is comparable with, but no better than, available antiemetics. Of great interest is the recent work of Greif and colleagues who showed that, after colonic resection, supplemental oxygen therapy reduced the incidence of PONV significantly.[17]

Clearly, many treatments are available for PONV but none can be described as a panacea. Combination drug therapy may be the answer. Amongst the first groups to demonstrate that a combination of antiemetics can be more effective that single drug therapy alone were those of McKenzie and colleagues[18] and Pueyo and co-workers.[19] For example, the latter showed that, after major gynaecological surgery, the incidence of a complete response to treatment (defined as no PONV in the first 48 h after surgery) in patients receiving placebo, droperidol 2.5 mg at induction of anaesthesia and droperidol 1.25 mg 12 h later, ondansetron 4 mg at induction of anaesthesia or a combination of droperidol and ondansetron at the same doses and time intervals was 28, 60, 56 and 92%, respectively. Only 8% of patients experiencing any degree of PONV during the first 48 h after major gynaecological surgery is very impressive indeed. Others have confirmed this phenomenon[11 20] but it is not a consistent finding. For example, a combination of ondansetron and droperidol was not superior

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to droperidol alone for the prevention of PONV in children undergoing strabismus surgery[21] or in adults after major gynaecological surgery.[22]

Clearly more work is required in this area and the article by Ahmed and colleagues investigating the efficacy of a combination of ondansetron and cyclizine published in this issue of the *British Journal of Anaesthesia* is a useful addition to the literature.[23] In a randomized, double-blind trial of 139 females undergoing day-case gynaecological laparoscopic surgery, patients were given at induction of anaesthesia either ondansetron 4 mg, ondansetron 4 mg and cyclizine 50 mg or saline. Compared with the ondansetron only group, there was a significantly decreased incidence of vomiting (11/59 *vs* 2/60, P=0.01) and need for rescue antiemetic (29/59 *vs* 2/60, P=0.03) in the combination group before discharge. There was also a significant decrease in the incidence and severity of nausea. The study would have been more elegant if a cyclizine only group had been included but the data are striking and add further weight to the suggestion that combination therapy may be the way forward.

We need considerably more data in this area but it seems likely that combination therapy may offer improved efficacy for the prevention, or even treatment, of PONV. Antiemetics may act at the dopamine (D_2), cholinergic, histamine (H_1), 5-HT_3 and NK_1 receptors and, when deciding upon a combination, it is logical to choose drugs acting at different receptors. The precise site of action of dexamethasone is, as yet, unclear.

Perhaps an analogy can be made between the present status of antiemetic therapy and that of postoperative pain relief approximately 10 yrs ago. At that time, we realized that the perfect analgesic was not likely to be forthcoming. We accepted the concept of inhibiting opioid receptors (opioid analgesics), cyclo-oxygenase (non-steroidal anti-inflammatory drugs) and neuronal sodium channels (local anaesthetics) with standard drugs in order to provide effective analgesia with an acceptable incidence of side-effects, i.e. balanced analgesia. The most effective combinations of antiemetics and their doses have yet to be elucidated but perhaps we should begin to embrace the concept of balanced antiemesis.

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CLINICAL INVESTIGATIONS

Randomized, placebo-controlled trial of combination antiemetic prophylaxis for day-case gynaecological laparoscopic surgery†

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In a randomized, double-blind trial, we compared i.v. ondansetron 4 mg (control), i.v. ondansetron 4 mg and cyclizine 50 mg (combination) and i.v. saline 0.9% (placebo), given after induction of standardized anaesthesia, for the prevention of nausea and vomiting (PONV) after day-case gynaecological laparoscopic surgery. Compared with placebo, fewer patients in the control group vomited (9/20 versus 11/59, P=0.02) or needed rescue antiemetic (7/20 versus 9/59, P=0.06) before discharge. Compared with the control, fewer patients in the combination group (n=60) vomited (11/59 versus 2/60, P=0.01) or needed rescue antiemetic (29/59 versus 2/60, P=0.03) before discharge. The incidence of vomiting in the combination group was less than 5% overall. Compared with the control, the combination group had a significantly lower incidence (P=0.001) and severity (P<0.001) of nausea after discharge and more patients with no PONV at any time during the study (15/59 versus 27/60, P=0.03). Unlike the placebo and control groups, no patient receiving combination prophylaxis was admitted overnight for PONV management.

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Postoperative nausea and vomiting (PONV) is associated with gender, motion sickness, opioids and previous PONV.[1–3] Its reported incidence after day-case gynaecological laparoscopic surgery exceeds 50%.[3–5] Postoperative nausea and vomiting is often the most distressing aspect of patients' surgical experience,[6] can increase pain and cause unplanned hospital admission.[7] As more patients undergo surgery as a day case, the humanitarian and economic implications of PONV are becoming increasingly important.[8]

Prophylaxis of PONV often consists of a single antiemetic drug given during surgery. Of those available, ondansetron,[4 5 9] cyclizine[10] and droperidol[11] reduce the incidence of PONV by approximately 50%. However, many patients continue to experience PONV. Therefore, a different strategy is required to solve this problem.

Before the advent of $5HT_3$ receptor antagonists, combinations of antiemetics were used for the management of patients at risk of chemotherapy-induced emesis.[12] The success of $5HT_3$ receptor antagonists in the field of cancer chemotherapy has, unfortunately, not been repeated for PONV. However, combination antiemetic prophylaxis is a promising approach for inpatient surgery.[13 14] We evaluated the efficacy of a combination of ondansetron and cyclizine for the prophylaxis of PONV in patients undergoing day-case gynaecological laparoscopic surgery.

Patients and methods

With hospital ethics committee approval and informed patient consent, we recruited patients aged 18 yr and over who were undergoing day-case gynaecological laparoscopy. Patients with a history of gastro-oesophageal reflux, taking medications with known antiemetic activity or who were pregnant or breastfeeding were excluded.

All received a standardized general anaesthetic. After induction with propofol 2–3 mg kg^{-1} and alfentanil 10 μg kg^{-1} and muscle relaxation with vecuronium 0.05–0.1 mg kg^{-1}, a laryngeal mask airway was inserted and the patient's lungs were ventilated mechanically to an end-tidal CO_2 of 4.5–5.0 kPa. Anaesthesia was maintained with 35% oxygen in nitrous oxide with added isoflurane. After induction, each patient was given i.v. morphine 0.18 mg kg^{-1} to a maximum of 12.5 mg and rectal diclofenac 100 mg for postoperative analgesia. At the end of

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surgery, muscle relaxation was reversed with neostigmine 2.5 mg and glycopyrrolate 500 μg.

We planned to study 150 patients in a double-blind manner. Patients were allocated randomly, using a closed envelope technique, in blocks of 50 to three groups in a 2:2:1 ratio to receive ondansetron 4 mg and 0.9% saline (control), ondansetron 4 mg and cyclizine 50 mg (combination) or 0.9% saline (placebo). Each treatment was given as two 10 ml i.v. injections. These were prepared by a single investigator who took no part in data collection.

After surgery, increments of i.v. morphine for severe pain, oral dihydrocodeine 60 mg for moderate pain and a rescue antiemetic (i.m. prochlorperazine 12.5 mg) for nausea or vomiting were given as judged necessary by one of two recovery nursing staff. Patients were discharged from the day-case unit when they were able to take oral fluids and walk independently. This decision required the agreement of both patient and nurse. Patients were given oral diclofenac 75 mg sustained release to be taken 12-hourly and oral dihydrocodeine 60 mg to be taken 4-hourly as required at home for pain.

Table 1 shows the patient characteristics and the clinical outcome data collected during the study. Clinical outcome data were assessed during three periods after surgery but before discharge: in the recovery area (0–30 min), in the day-case ward (30–120 min) and in the postoperative sitting room (120–240 min). The assessments were made at the end of each timing interval, and the worst score during each interval for each symptom was recorded. The severities of nausea and pain were assessed by the patients, using standard four-point ordinal scales (none, mild, moderate, severe). The single worst scores for nausea and pain from any of the three time periods before discharge were used for analysis. Data from patients who completed the study up to hospital discharge or admission were included.

A telephone questionnaire was completed by the patients 24 h after surgery. This assessed the incidence of vomiting, the incidence and severity of nausea and pain, and analgesic requirements during the 24 h after hospital discharge, including the journey home. Similarly, the worst severity of nausea was taken to be the end-point in the post-discharge analysis. Data from patients admitted to hospital or receiving rescue antiemetic were excluded from the analysis of post-discharge data. All data were recorded by a single research nurse who remained blinded to the treatment groups throughout the study.

The major outcome measures were the incidences of vomiting before and after discharge, the need for rescue antiemetic before discharge and the frequency of a complete response (defined as the absence of any nausea and vomiting during the whole study period). Continuous data were analysed using Student's *t*-test and ANOVA. Other data were analysed with the χ^2 and Fisher's exact sum tests if contingency tables had insufficient numbers. Pairwise comparisons of data before discharge were performed if there was an overall difference at the 5% level. After discharge, data from control and combination groups only were compared. Data were analysed using Minitab for Windows, release 10.1. Using previously published data from similar patient groups and local clinical audit, a 50% reduction in the incidence of vomiting after the combination treatment compared with the control, and control compared with placebo, would be demonstrated using a sample size of 150 patients in a 2:2:1 ratio respectively, with a power in excess of 0.8 at α=0.05. P<0.05 was taken as statistically significant.

Table 1 Patient characteristics and clinical outcome BMI = body mass index, *major outcome measures

Patient characteristics
- Age
- BMI
- Previous history of PONV
- Previous history of motion sickness
- Date of last menstrual period
- Type of laparoscopy (diagnostic or sterilization)

Clinical outcome
- Pain, incidence and severity
- Postoperative analgesic requirements
- Nausea, incidence and severity
- Vomiting, incidence*
- Need for rescue antiemetic before discharge*
- Need for overnight hospital admission
- Complete response (no PONV at any time)*

Results

During the conduct of this study, we demonstrated in another study in a similar patient group that both cyclizine and ondansetron given singly were better than placebo for the prophylaxis of PONV.[10] We therefore undertook interim analysis of the first 100 patients, which confirmed a significantly higher incidence of PONV in patients receiving placebo. Allocation to this group was therefore discontinued and 140 patients were finally enrolled in the study.

One patient who underwent laparotomy (control group) was withdrawn from the study. Data before discharge from 139 patients were analysed (Table 2). All groups were comparable for patient characteristics, pain and analgesic requirement. No patient required the administration of atropine or glycopyrrolate for intra-operative bradycardia. Eighteen patients (Fig. 1) received rescue antiemetic in hospital (seven in the placebo group, nine in the control group and two in the combination group) Seven were admitted overnight for management of PONV or four for other reasons (uncontrolled pain, surgical observation or social reasons). Table 3 gives the data for the remaining 110 patients who completed the telephone questionnaire at 24 h. Patient characteristics and analgesic data after discharge were comparable for the control and combination groups. There were more patients with moderate or severe pain in the control group, but this did not reach statistical significance. Two patients in this group received postoperative morphine, as did two in the combination group and none in

Table 2 Patient characteristics and clinical outcome before discharge *Mean (SD), otherwise number (%) of patients BMI=body mass index

Variable	Control group (n=59)	Combination group (n=60)	Placebo group (n=20)	P
Patient characteristics				
Age (yr)*	34 (7)	32 (6)	31 (5)	0.22
BMI (kg m^{-2})*	25 (3)	25 (4)	24 (4)	0 78
Previous PONV	21 (36)	22 (37)	10 (50)	0.494
Previous motion sickness	23 (39)	23 (38)	8 (40)	0 991
Menstrual cycle day*	14 (9)	15 (12)	14 (9)	0.990
Laparoscopy type				0.470
Diagnostic	37 (63)	32 (53)	10 (50)	
Sterilization	22 (37)	28 (47)	10 (50)	
Clinical outcome				
Moderate or severe pain at any time	28 (48)	34 (57)	11 (55)	0.586
Nausea at any time	12 (20)	10 (17)	6 (30)	0 436
Moderate or severe only	11 (19)	4 (7)	5 (25)	0.061
Overnight admission for PONV	4 (7)	0 (0)	3 (15)	–

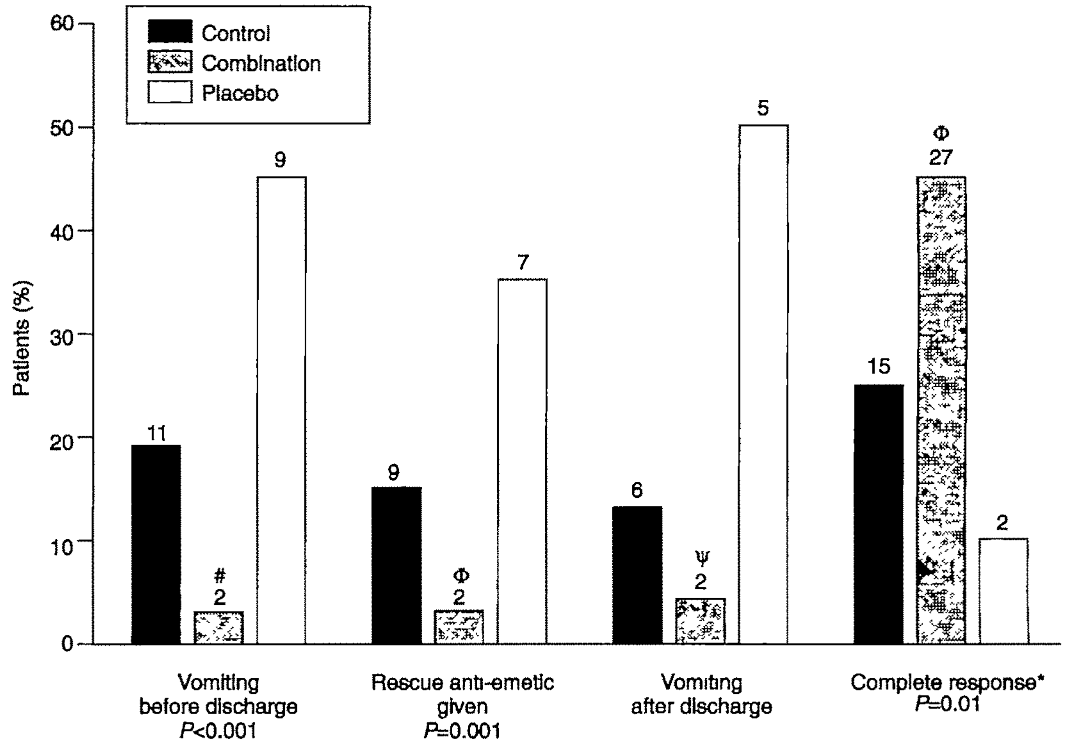

Fig 1 Primary outcome measures. Numbers over bars are number of patients. *Complete response = no nausea or vomiting at any time. The P values in the figure refer to comparisons between all groups. Combination compared with control: $^{\#}P$=0.01; $^{\Phi}P$=0.03; $^{\Psi}P$=0.08

the placebo group. This factor was, therefore, unlikely to be of significance.

Figure 1 shows data for the major outcome measures. Compared with the placebo group, the control group had a significantly lower incidence of vomiting (P=0.02). Compared with the control group, the combination group had significantly less vomiting (P=0.01) and need for rescue antiemetic (P=0.03) before discharge, tended to vomit less after discharge (P=0.08) and had a significantly greater number of patients with a complete response (P=0.03). The incidence of vomiting in the combination group was less than 5% overall.

Compared with the control group, the combination group tended to have a lower incidence of moderate or severe nausea before discharge (P=0.06), and a significantly lower incidence and severity of nausea after discharge. No patients in the combination group required overnight admission for the management of PONV.

Discussion

We have demonstrated, as have others,[4 5 9] that in patients undergoing day-case gynaecological laparoscopy the prophylactic administration of ondansetron significantly

Table 3 Patient characteristics and clinical outcome data after discharge. *Mean (SD), otherwise number (%) of patients; [§]comparison between control and combination groups. BMI=body mass index

Variable	Control group (n=45)	Combination group (n=55)	P[§]	Placebo group (n=10)
Patient characteristics				
Age (yr)*	33 (7)	32 (6)	0.43	31 (5)
BMI (kg m^{-2})*	25 (4)	25 (4)	0.57	24 (4)
Previous PONV	16 (36)	21 (38)	0.79	7 (70)
Previous motion sickness	19 (42)	23 (42)	0.97	6 (60)
Menstrual cycle day*	18 (21)	17 (16)	0.74	15 (9)
Laparoscopy type			0.34	
Diagnostic	28 (62)	29 (53)		5 (50)
Sterilization	17 (38)	26 (47)		5 (50)
Clinical outcome				
Moderate or severe pain at any time	21 (47)	16 (29)	0.07	3 (30)
Nausea at any time	22 (49)	10 (18)	0.001	9 (90)
Moderate or severe only	17 (38)	4 (7)	<0.001	6 (60)
During the journey home				
Any nausea	21 (47)	8 (15)	<0.001	6 (60)
Moderate or severe nausea	8 (18)	2 (4)	0.02	3 (30)
Vomiting	5 (11)	2 (4)	0.145	4 (40)

reduces the problem of PONV. When cyclizine was combined with ondansetron, this reduction was even more striking, the effect extending into the period from discharge, through the journey home to the day after surgery.

Patients undergoing day-case gynaecological laparoscopy have a number of risk factors for PONV, including female gender, the use of per-operative opioids[15] and a journey home likely to lower the threshold to motion-induced emesis.[16] Consequently, we believe that this group provides an excellent model for antiemetic studies.

Ondansetron has few unwanted side-effects.[9] It has been given prophylactically in combination with dexamethasone in major gynaecological surgery[13] and with droperidol in females using patient-controlled analgesia with morphine after abdominal surgery.[14 17] These inpatient studies suggest that combination prophylaxis may be associated with significant improvements in PONV outcomes. However, the extrapyramidal side-effects of droperidol are of some concern, particularly in day-case patients,[18] and many clinicians may be reluctant to give steroids primarily for managing PONV. Cyclizine is an alternative antiemetic and is efficacious for the prevention of PONV after day-case gynaecological surgery.[10] When given sequentially for treating established PONV after major surgery, ondansetron and cyclizine together may be more effective than either drug alone.[19] Cyclizine causes mild sedation, which is unlikely to be of significance, and tachycardia; the advantage of this is arguable because dangerous bradycardia may accompany the pneumoperitoneum that accompanies laparoscopy. It is an antagonist at muscarinic cholinergic and histamine-1 receptors.[20] Its combination with a $5HT_3$ antagonist is entirely logical, given the multi-receptor aetiology of PONV.[6] Cyclizine is also inexpensive.

Our study could be criticized on a number of grounds. First, we used morphine per-operatively, a recognized cause of PONV.[3] However, gynaecological laparoscopy, particularly when clips are applied to the Fallopian tubes, causes pain.[21] A departmental audit in this patient group indicated a higher risk of unacceptable pain before and after discharge when morphine was omitted from the analgesic regimen. Furthermore, there is an association between pain and PONV,[22] and treating pain with opioids may relieve PONV.[22 23] Our use of morphine was deliberate, and this accords with a recent survey of routine practice.[15] Secondly, we did not stratify patients for the nature of the gynaecological procedure. We have previously suggested that the efficacy of single antiemetic prophylaxis may be influenced by the type of laparoscopic operation performed.[10] However, the types of laparoscopy performed (diagnostic or sterilization) in our study were comparable between groups and this factor was unlikely to have influenced our results. Thirdly, we identified neither those at particular risk of PONV[2] nor those who smoked. It was therefore inevitable that some patients who may not have suffered PONV received unnecessary antiemetic therapy. However, we believe the high risk of PONV in this group of patients justifies aggressive prophylaxis. Fourthly, we abandoned allocation to the placebo group when one of our studies[10] demonstrated the superiority of both cyclizine and ondansetron over placebo when given prophylactically in a similar patient population. We felt obliged to perform interim analysis of the current study, and when it revealed a similar result we took advice and on ethical grounds stopped allocating to the placebo group. Some may also be critical of the use of placebo in studies of PONV.[24] In order to validate our model of PONV and strengthen our study design, we considered it desirable to demonstrate concurrently the efficacy of single and combination prophylaxis. Finally, we did not collect side-effect data. It was the aim of this study to establish only the efficacy of combination prophylaxis after day-case surgery.

Many studies of antiemetics show significant reductions in the incidence of PONV, often of the order of 50%,[4 5 9 11] but the outcomes associated with single antiemetic prophylaxis remain disappointing. A recent systematic review of the use of ondansetron compared with placebo for the prevention of PONV estimated the 'number needed to treat' (the number of patients that must be exposed to a treatment to prevent one PONV event) to be 5–6 when the risk of PONV was high.[25] The authors challenged the use of prophylactic ondansetron when risk–benefit and cost–benefit arguments were considered. A randomized, double-blind, placebo-controlled study comparing the efficacy and costs of droperidol or ondansetron for PONV prevention in a patient group similar to that taking part in our study concluded that the use of low-dose droperidol was more cost-effective.[11] However, the incidences of vomiting after low-dose droperidol were 12 and 27% before and after discharge respectively. The corresponding incidences after combination prophylaxis in our study were 3 and 4% respectively.

If our results are confirmed in other day-case studies, then combination therapy represents a major step forward in improving the outcome in these patients. It is important, especially in this group of patients, to have effective control of symptoms. Combination prophylaxis may also have important economic implications. These include reduced costs associated with nursing time spent managing PONV as well as the costs of delayed discharge or unplanned admission. Appropriate economic evaluations of these and alternative antiemetic combinations need to be performed for different patient groups, including the assessment of side-effect profiles, and there is a need to verify our results in day-case patients. Data concerning single antiemetic prophylaxis may therefore no longer be clinically relevant in patient groups at high risk of PONV.

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Pharmacokinetics and pulmonary extraction of clevidipine, a new vasodilating ultrashort-acting dihydropyridine, during cardiopulmonary bypass[†]

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Clevidipine is a new vascular-selective, calcium channel antagonist of the dihydropyridine type with an ester side chain susceptible to esterase metabolism. In healthy volunteers, it has high clearance (0.069 litres min^{-1} kg^{-1}) with a small volume of distribution at steady state (0.19 litres kg^{-1}). The half-lives of the two initial rapid phases, accounting for approximately 95% of the area under the curve after an i.v. bolus, are 0.7 and 2.3 min, respectively. The aims of this study were to determine the pharmacokinetics and the pulmonary extraction ratio of clevidipine in patients undergoing cardiac surgery. Seventeen patients received clevidipine as an i.v. infusion before cardiopulmonary bypass (CPB), and eight of these patients were also given clevidipine during hypothermic CPB. Mixed venous and arterial blood samples were taken for pharmacokinetic analysis and calculation of pulmonary extraction ratio. A two-compartment pharmacokinetic model with zero-order input was used to describe the pharmacokinetics of clevidipine before and during CPB. Virtually identical concentrations in mixed venous and arterial blood suggest negligible pulmonary metabolism of clevidipine. The total blood clearance of clevidipine is extremely high (0.055 litres min^{-1} kg^{-1}). During CPB, clearance of clevidipine was significantly reduced, to 0.03 litres min^{-1} kg^{-1} ($P<0.005$), probably as a consequence of reduced body temperature.

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An important aspect of cardiac anaesthesia is to maintain haemodynamic stability while patients are subjected to stimuli of various intensities.[1] However, the anaesthetic regimen may not predictably attenuate the haemodynamic response to various stimuli in patients undergoing coronary revascularization, whether they are based on high doses of opioids or balanced techniques.[2] Moreover, postoperative hypertension is a common event after coronary artery bypass grafting (CABG) surgery and is associated with subendocardial ischaemia,[3–5] bleeding and cerebrovascular haemorrhage.[6–8]

Of the drugs available to control and reduce arterial pressure during cardiac surgery, calcium antagonists, such as nicardipine, may be beneficial because of their favourable haemodynamic profile.[9 10] However, the pharmacokinetic properties of these agents render their clinical use more difficult than that of other drugs, such as glyceryl trinitrate and sodium nitroprusside, whose effects can be easily controlled because of their very short half-lives and the predicted post-infusion decline in plasma concentration after various lengths of infusion.[11 12]

Clevidipine is a new vascular-selective calcium channel antagonist of the dihydropyridine type.[9 13] It is structurally related to another calcium antagonist, felodipine, but, because it contains an ester linkage, is rapidly metabolized by esterases in blood and extravascular tissues to its inactive carboxylic acid metabolite.[14 15] Clevidipine is cleared quickly with a relatively small volume of distribution resulting in an extremely short half-life in healthy volunteers, essential hypertensive and postcardiac surgical patients.[13 15–18] *In vitro* studies have shown that the elimination of clevidipine is reduced at lower blood

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temperatures.[14] This suggests that elimination of clevidipine might be reduced during hypothermia *in vivo*, as are other ester-containing molecules, such as remifentanil and esmolol, which both have decreased clearance during hypothermic cardiopulmonary bypass (CPB).[19 20]

Although clevidipine has previously been shown to reduce and control arterial pressure effectively in essential hypertensive and anaesthetized patients after cardiac surgery,[17 18] this was the first study in which clevidipine was administered to patients during cardiac surgery. The aims of this study were to determine the pharmacokinetics of clevidipine before and during hypothermic CPB and to determine the pulmonary extraction of clevidipine in patients undergoing CABG surgery.

Patients and methods

Following approval by the Local Research Ethics Committee, 20 patients were enrolled after giving written informed consent. All patients were scheduled for elective CABG surgery. The main exclusion criteria for taking part in the study were acute myocardial infarction within 30 days before the study, an ejection fraction of ≤0.35, heart rate ≥120 beats min^{-1} and clinically significant hepatic or renal disease.

Antihypertensive treatment, except for beta-blockers, was stopped the night before surgery. All patients received a standardized anaesthetic regimen consisting of morphine 10–15 mg i.m. and scopolamine 0.2–0.4 mg i.m. as premedication, followed by midazolam 0.1 mg kg^{-1}, fentanyl 15 μg kg^{-1} and pancuronium 0.15 mg kg^{-1} i.v. for induction of anaesthesia, and isoflurane at a minimum of 1% end-tidal concentration for maintenance of anaesthesia. Isoflurane was administered in 60% oxygen and 40% air when off CPB and the oxygen/air ratio was adjusted to the best blood gases during CPB (α-stat management of pH).

All patients underwent mild hypothermic CPB (30°C) with standardized equipment, and diastolic cardiac arrest was induced with cold crystalloid cardioplegia. The CPB circuit was primed with 1.5 litres of crystalloid solution. A roller pump (Cobe Laboratories, Denver, CO, USA) generated non-pulsatile flow, and the flow rate during the hypothermic phase of CPB was 1.8 litres min^{-1} m^{-2}. Blood was circulated through a hollow fibre membrane oxygenator (Maxima^{PRF} T; Medtronic, Anaheim, CA, USA) and gas flow was adjusted in order to maintain arterial blood at pH 7.4 (α-stat measurement). Catheters were inserted into the left radial artery (Insyte® Vialon® Becton Dickinson, Franklin Lakes, NJ, USA) and pulmonary artery (Swan-Ganz 7F; Baxter Healthcare Corporation, Irvine, CA, USA) via the right subclavian vein. Heart rate and arterial pressure were monitored for ≤15 h from the start of anaesthesia. Nasopharyngeal temperature and haematocrit were also recorded throughout surgery.

Clevidipine is a 20% lipid emulsion containing clevidipine 0.5 mg ml^{-1}. Syringes containing clevidipine were connected to a filter (Sterifix 5 μm; Braun, Melsungen, Germany) and a 15 cm extension line (polyethylene extension tube 15 cm; Vygon, Ecouen, France). The drug was infused into the right jugular vein by means of a calibrated syringe driver (P1000 syringe pump, Welmed; Braun Melsungen). An infusion of clevidipine was started if the mean arterial pressure (MAP) exceeded 90 mm Hg before CPB or 75 mm Hg during CPB. The starting rate was 0.7 μg kg^{-1} min^{-1} and the maximum rate allowed was 22 μg kg^{-1} min^{-1}. The infusion rates were adjusted every 2 min in steps according to the judgement of the investigator in order to reduce arterial pressure to the target MAP (i.e. 70–75 mm Hg before CPB and 55–60 mm Hg during CPB). When the desired MAP was reached, the clevidipine infusion was kept constant for ≥10 min and then stopped. Sodium nitroprusside was used to control arterial pressure after cessation of the clevidipine infusion. If clevidipine was infused before CPB, the clevidipine infusion was interrupted for ≥20 min before starting CPB in order to allow a washout period of clevidipine.

Blood sampling and bioanalysis

Blood samples (2 ml) for clevidipine analysis were drawn from the left radial artery before infusion, at 8, 9 and 10 min of constant rate infusion and 0.5, 0.75, 1, 2, 3, 4, 6, 8 and 10 min after termination of the infusion. Arterial pulmonary blood samples were taken at 8, 9 and 10 min of constant rate infusion. In addition, blood samples were taken at 5 and 9 min of constant rate infusion from the in-flow (venous side) and out-flow (arterial side) of the CPB circuit.

The collected blood was rapidly transferred to pre-weighed test tubes containing 2 ml of 10% sodium dodecyl sulphate (SDS) which, on mixing, immediately stops hydrolysis of clevidipine.[21] The samples were weighed and frozen within 1 h and stored at −70°C until analysis. The clevidipine concentrations were determined by a method based on gas chromatography/mass spectrometry.[22] The linearity of the method during the assay period was estimated from five standard curves. The standard curves were linear within the concentration range 0.26–166 μg $litre^{-1}$. The mean intra-day coefficients of variation (CVs) of blood standards of clevidipine were 2.2–14.6% at 0.25 μg $litre^{-1}$ and 1.1–2.9% at 16.5 μg $litre^{-1}$. The lower limit of quantitation was set at 0.23 μg $litre^{-1}$.

Pharmacokinetic analysis

The population mean pharmacokinetic parameters of clevidipine were determined by non-linear mixed effect modelling using the software program P-PHARM (version 1.5; SIMED, Creteil, France).[23] The time course of the clevidipine concentrations in the arterial blood was fitted to mono-, bi-, or tri-exponential disposition functions.

Initial analyses of the distribution of the residuals showed that the error variance was best described by a hetereoscedastic model ($1/C^2_{\text{pred}}$ where C_{pred} is the predicted concentration) and this error model was used in all analyses. The goodness of fit was evaluated by the Akaike information criterion, log-likelihood values and visual inspection of residual plots. The blood clearance (Cl_b), initial volume of distribution (V_1) and the rate constants for drug transfer between the central and the peripheral compartment(s), k_{12} and k_{21}, were considered as primary parameters with normal distribution. Thus, the population mean and an estimate of its variability were obtained for each of these parameters. Other reported pharmacokinetic parameters were calculated from the individual (Bayesian) parameter estimates using standard pharmacokinetic equations.[24] In addition, steady-state blood clearance ($Cl_{b,ss}$) was calculated as R_o/C_{ss}, where R_o was the infusion rate and C_{ss} the steady-state concentrations calculated as the mean of the clevidipine concentrations during the infusion.

Pulmonary extraction was calculated by dividing the difference between mean pulmonary and mean radial artery clevidipine concentrations by the pulmonary artery concentrations and expressing the results as a percentage for each patient. The mean concentrations were calculated from all blood concentrations obtained during the clevidipine infusion.

Statistics

The population mean pharmacokinetic parameters were estimated for the patients treated before (n=17) and during CPB (n=8). In order to compare the individual pharmacokinetic parameters before and during CPB, the statistical analysis was restricted to the eight patients who received clevidipine both before and during CPB. The pharmacokinetic parameters were analysed by paired Student's t-test; P<0.05 was considered significant. Results are expressed as mean (SD).

Results

Twenty patients undergoing CABG were enrolled in this study. In three patients, arterial pressure did not rise above the inclusion level; thus, 17 patients completed the treatment and were evaluated regarding the pharmacokinetics of clevidipine. Eight of these were also treated with clevidipine during CPB. The pulmonary extraction ratio was only determined in 16 patients since blood sampling was accidentally omitted in one patient. The minimum infusion time was 10 min and the actual infusion time was 10, 11 or 13 min. However, blood samples for clevidipine determination were always collected 10 min after infusion. The physical characteristics of the patients are shown in Table 1.

Table 1 Physical characteristics of the 17 patients studied; mean (SD) values are given for age, height, weight and body mass index (BMI)

	All patients	During CPB
Gender: males/females	14/3	6/2
Age (years)	62 (44–76)	65 (44–76)
Height (cm)	174 (6)	173 (7)
Weight (kg)	81 (14)	75 (16)
BMI (kg m^{-2})	27 (4)	25 (5)
Beta-blocker treatment	11	6

A bi-exponential disposition model was used to describe the pharmacokinetics of clevidipine before and during CPB. The mean population fit and the individual fit of this model to the data obtained from patients before CPB (n=17) are shown in Figure 1(A), where the data are normalized to a dose rate of 1.4 μg kg^{-1} min^{-1}. The population-predicted versus observed clevidipine concentrations are shown in Figure 1(B). The corresponding plots for the eight patients treated with clevidipine during CPB are shown in Figure 1(C) and the goodness of fit in Figure 1(D). The individual fits, based on Bayesian parameter estimate, of a two-compartment model to the clevidipine concentration–time data in patients receiving clevidipine both before CPB and during hypothermic CPB (n=8) are given in Figure 2.

The mean pharmacokinetic parameters of clevidipine determined in all patients before CPB and in the patients receiving clevidipine both before and during hypothermic CPB are given in Table 2. Mean (SD) Cl_b during CPB (0.03 (0.005) litres min^{-1} kg^{-1}) was significantly lower than that before CPB (0.058 (0.014) litres min^{-1} kg^{-1}), whereas mean (SD) V_{ss} was similar under both conditions (0.11 (0.04) and 0.12 (0.03) litres kg^{-1}, respectively). As a consequence of the reduced clearance and the unchanged volume of distribution, the resulting half-lives were significantly longer during hypothermic CPB than during CPB. The α and β half-lives of clevidipine were 0.6 (0.2) and 3.8 (0.2) min before CPB and 1.3 (0.5) and 7.5 (1.1) min during CPB, respectively.

The individual mean radial and pulmonary artery concentrations obtained during clevidipine infusion are shown in Figure 3. The pulmonary extraction ratio was 3.9 (8.3) %, suggesting negligible or no pulmonary metabolism of clevidipine. In addition, there was no extraction of clevidipine by the extracorporeal circuit, since the difference in clevidipine concentration between the aortic and venous cannulae of the CPB circuit was 1.5 (4.7) and −1.4 (3.9) μg litre^{-1} at 5 and 9 min, respectively.

Before CPB, the MAP at the start of treatment was 97 (6) mm Hg, and during CPB, the mean (SD) MAP at the start of treatment was 73 (10) mm Hg. Treatment was started during CPB in one patient at 72 mm Hg as this was judged clinically appropriate.

The infusion rate required to control arterial pressure before CPB and during hypothermic CPB was 2.2 (0.9) and 1.3 (0.4) μg kg^{-1} min^{-1}, respectively.

Before CPB, the heart rate was 72 (13) and 75 (17) bpm, before and at the end of clevidipine infusion, respectively. There was no difference in heart rate response whether or not the patient was treated with a beta-blocker (n=11 and n=6, respectively).

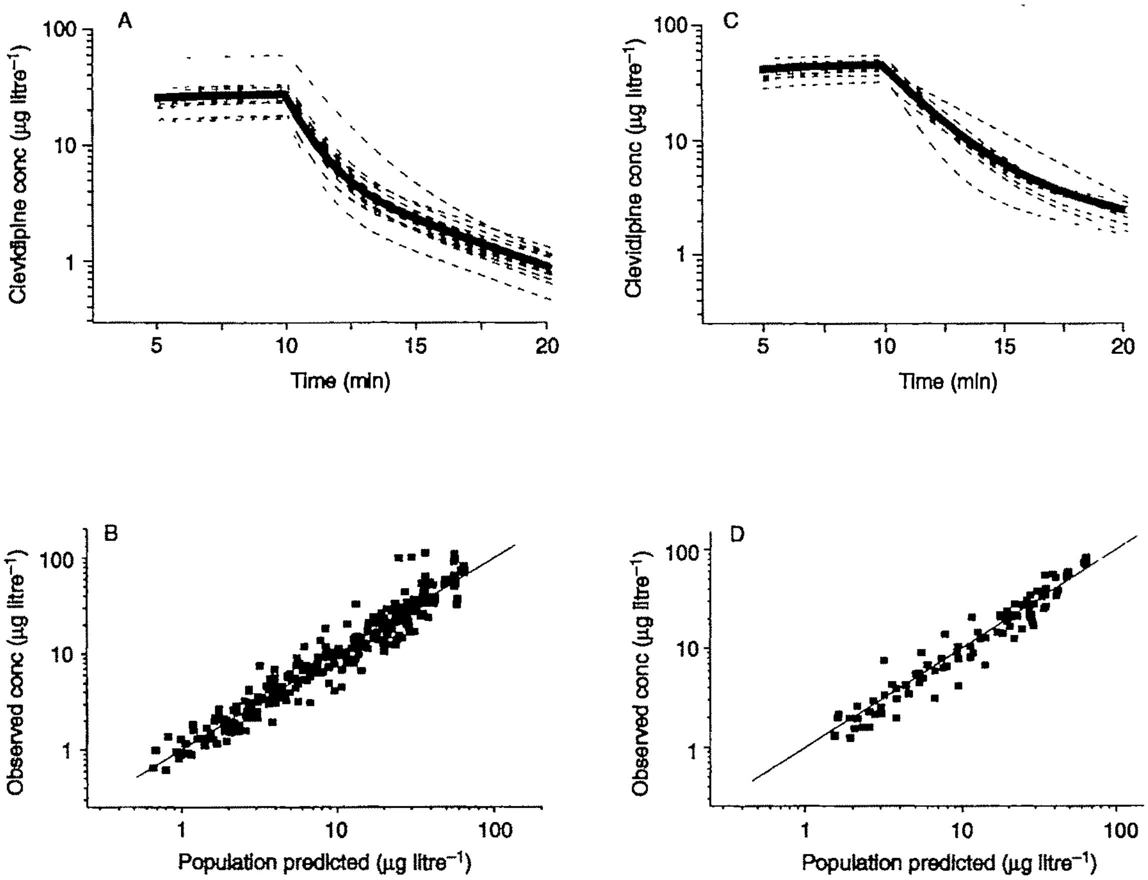

Fig 1 The mean population fit (thick black line) and the individual fit (dashed lines) of a two-compartment model to the clevidipine concentration–time data (A) before CPB (n=17) and (C) during hypothermic CPB. The data are dose-normalized to a dosing rate of 1.4 μg kg^{-1} min^{-1} over a 10 min period. The goodness of fit is shown for data before CPB (B) and during CPB (D) and the solid line represents line of identity

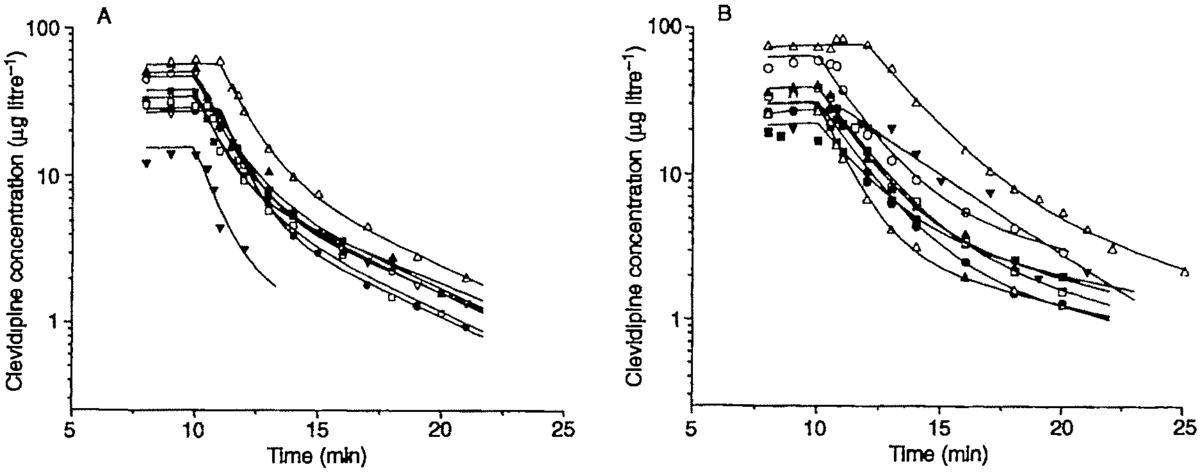

Fig 2 Observed blood concentration of clevidipine and the model-predicted concentrations, in eight patients receiving clevidipine before CPB (A) and during hypothermic CPB (B). Each symbol in both graphs represents the same patient and the solid lines show the fit, based on Bayesian parameter estimate, of the model to the data. In one patient (open triangle) in which infusion lasted for 13 min, more than the recommended number of blood samples were taken and all concentrations were included in the analysis.

During bypass, nasopharyngeal temperature decreased from 34.9 (0.5) °C to 30.8 (1.5) °C, and the haematocrit decreased from 34 (5) % to 28 (4) % because of haemodilution.

Table 2 The mean and SD pharmacokinetic parameters, calculated from Bayesian parameter estimates and steady-state concentrations, of clevidipine determined in all 17 patients before CPB (A) and in the eight patients receiving clevidipine both before (B) and during (C) hypothermic CPB, AUCα is the contribution of the initial AUC to the total area following a unit i.v dose; * ** significantly different from pre-CPB (*$P<0.05$, **$P<0.005$)

		Clb (litres min^{-1} kg^{-1})	k12 (min^{-1})	k21 (min^{-1})	V1 (litres kg^{-1})	VSS (litres kg^{-1})	t1/2α (min)	t1/2β (min)	AUCα (%)	CLb,ss (litres min^{-1} kg^{-1})
A	mean	0.055	0.168	0.226	0.06	0.11	0.7	3.8	76.9	0.059
	SD	0.014	0.049	0.005	0.01	0.03	0.1	0.2	4.2	0.011
B	mean	0.058	0.180	0.227	0.07	0.12	0.6	3.8	75.2	0.060
	SD	0.014	0.043	0.004	0.01	0.03	0.2	0.2	3.1	0.011
C	mean	0.030**	0.069**	0.108**	0.07	0.11	1.3*	7.5**	83.5*	0.037**
	SD	0.005	0.036	0.010	0.03	0.04	0.5	1.1	6.7	0.009

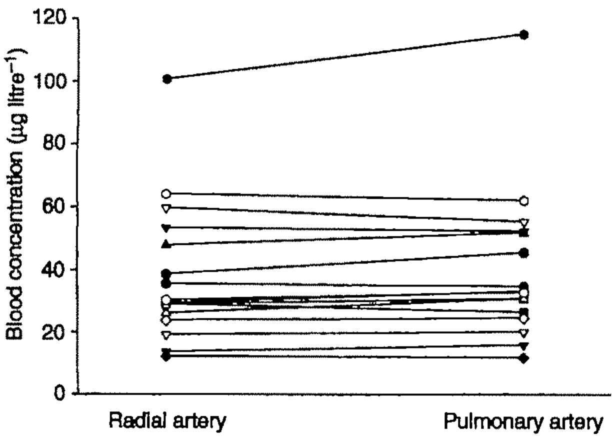

Fig 3 Individual pulmonary (mixed venous) and radial artery blood concentrations of clevidipine during the clevidipine infusion (n=16). Values are the means of three determinations in each patient during clevidipine infusion.

Discussion

Haemodynamic variations are common during cardiac surgery, as surgical stimuli will vary dramatically throughout the operation.[3 5] The use of short-acting drugs to control arterial pressure during cardiac surgery has practical advantages. It allows rapid titration to the desired effect, as the drug rapidly attains steady-state concentrations in the blood after initiation of an i.v. infusion.[11 12] Furthermore, the effect on arterial pressure is negligible shortly after termination of the infusion, which may obviate the need for vasopressors to compensate for the remaining vasodilating effect.[11]

All calcium antagonists currently used in perioperative care have been developed for oral use. As a class, the dihydropyridines exert reasonably homogeneous haemodynamic effects, which are of importance in the treatment of angina pectoris, hypertension and cardiac failure. However, attention has not been focused on the development of calcium antagonists with a pharmacokinetic profile suitable for controlling the rapid changes in arterial pressure that may occur during cardiac surgery.

Clevidipine is a new ultrashort-acting dihydropyridine calcium antagonist developed for controlling arterial pressure during cardiac surgery.[9 18] It is metabolized by blood and tissue esterases and its short half-life has been confirmed in both *in vitro* studies and in humans.[13–18]

The pharmacokinetics of clevidipine calculated from arterial blood concentrations before CPB in the present study were in agreement with the pharmacokinetic parameters reported for clevidipine in normothermic patients after CABG surgery and in healthy volunteers after arterial blood sampling.[16 18] Blood clearances calculated from the steady-state concentrations of clevidipine and the model-dependent estimate were virtually identical before CPB, whereas the model-dependent estimated blood clearance was slightly lower than that determined from steady-state concentrations during CPB. Plausible explanations for the discrepancy in the clearance value during CPB may be the short sampling period or that steady state was not achieved, or both. The latter seems unlikely since the arterial blood concentrations of clevidipine are at steady state within 2 min of starting an infusion in healthy subjects.[16] However, the reduction in blood clearance of clevidipine during hypothermic CPB is in agreement with *in vitro* studies in human blood, in which the *in vitro* half-life increased from approximately 6 min at 37°C to 11 min at 30.5°C.[14] In the same study, diluting the blood with an equal amount of Ringer–glucose solution did not affect the *in vitro* half-life of clevidipine in human blood,[14] suggesting that the reduced clearance during CPB is mainly a result of reduced temperature, and not of haemodilution during this procedure. However, factors such as the non-pulsatile flow generated by CPB equipment, reduced cardiac output and a corresponding change in perfusion may also contribute to the lower blood clearance of clevidipine during CPB.[25] Interestingly, the blood concentrations needed to control arterial pressure during the different phases of cardiac surgery were approximately the same, that is the lower dose rate needed during CPB was caused by the reduced clearance of clevidipine.

As clevidipine undergoes extensive extravascular metabolism, the use of a two-compartment model with elimination only from the central compartment might be schematically incorrect, and we cannot exclude the possibility of peripheral hydrolysis of clevidipine. A model allowing elimination from both the central and peripheral compartment would probably predict a larger volume of distribution at steady state.[26] However, without *a priori* knowledge of the exit rate constants from such a model, it is not possible to estimate the volume of distribution at steady state,[27] since such a model is mathematically indistinguishable from the classic two-compartment mammillary model with elimination only from the central compartment. Irrespective of the model fitted to the blood concentration–time profiles of clevidipine, the estimate of blood clearance will not be affected.[28]

The contribution of blood metabolism of clevidipine to the total elimination is <10%, indicating high esterase activity in extravascular tissues.[15] The present study suggests that extraction in the lungs is negligible, thereby ruling out the lungs as a major organ of eliminination of clevidipine. These results are also in agreement with the ultrashort-acting opioid remifentanil, which is not extracted by the pulmonary circulation.[25] As the blood clearance is approximately three times the average liver blood flow and close to the cardiac output in healthy subjects, other tissues besides the liver are likely to contribute to the elimination of clevidipine. Results from studies with the ester-containing compounds remifentanil and cisatracurium have indicated that liver impairment does not affect the total elimination of these drugs.[29 30]

In healthy volunteers, arterial pressure reduction caused by clevidipine is accompanied by an increase in heart rate,[13 15 16] but that was not reported in anaesthetized patients after cardiac surgery.[18] In the present study, there was no increase in heart rate when arterial pressure was reduced by clevidipine. This was true even in patients who were not receiving beta-blocker pretreatment, in whom a baroreceptor reflex-mediated change in heart rate could have occurred. The lack of heart rate increase during arterial pressure reduction in anaesthetized cardiac surgery patients but not in conscious volunteers is likely to be a result of depressed baroreceptor reflex sensitivity during anaesthesia.[31]

In conclusion, clevidipine has high clearance and effectively controls arterial pressure during CABG surgery both before and during hypothermic CPB. A higher dosing rate of clevidipine is required to control arterial pressure before CPB than during hypothermic CPB, probably as a consequence of reduced clearance of clevidipine during hypothermia.

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Conflict of interest

H. Ericsson, Å. Jolin-Mellgård and M. Nordlander are employees of AstraZeneca R&D Mölndal. This work was supported financially by AstraZeneca.

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Intravenous amiodarone or magnesium sulphate is not cost-beneficial prophylaxis for atrial fibrillation after coronary artery bypass surgery

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Our aims were to examine whether the administration of amiodarone or magnesium sulphate after coronary artery bypass graft surgery (CABG) could reduce the occurrence of atrial fibrillation, and to identify the risk factors associated with atrial fibrillation after CABG. Patients scheduled for elective CABG (n=155) were allocated randomly, in a controlled double-blind study, to receive immediately after surgery a 72-h infusion of amiodarone (900 mg per 24 h), magnesium (4 g per 24 h) or placebo (0.9% NaCl; 50 ml per 24 h) intravenously. A 72-h Holter ECG was recorded concomitantly. The primary end-point was the prevention of atrial fibrillation; its onset was considered as prophylactic failure. An interim safety analysis was performed in 147 patients. The cumulative occurrence of atrial fibrillation was 27% in the placebo group, 14% in the amiodarone group (P=0.14) and 23% in the magnesium group (P=0.82). Although amiodarone delayed the onset of the first tachyarrhythmic episode (P=0.02), it was associated with the need for longer periods of vasoactive drug infusion and invasive monitoring and a longer stay in the intensive care unit. Variables associated with the onset of atrial fibrillation were older age (odds ratio 1.9) and a plasma magnesium concentration at 24 h of less than 0.95 mmol litre^{-1} (odds ratio 6.7). Postoperative administration of amiodarone reduced the occurrence of atrial fibrillation after elective CABG surgery, but was associated with a longer duration of cardiovascular instability and longer need for intensive care; magnesium prophylaxis had no effect. Advanced age and a low plasma magnesium concentration are risk factors for postoperative atrial fibrillation.

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Cardiac arrhythmias occur in 11–40% of patients after coronary artery bypass graft (CABG) surgery, atrial fibrillation (AF) being the most common supraventricular arrhythmia.[1 2] Postoperative AF has a negative effect in terms of perioperative morbidity (myocardial infarction, stroke), 30-day and 6-month mortality, stay in the intensive care unit (ICU) and hospital costs.[3–7] Perioperative intravenous[8 9] or oral amiodarone[10] has been shown to decrease the occurrence of AF after cardiac surgery. Magnesium prophylaxis for postoperative AF has also been reported, with conflicting conclusions.[11–14] The aim of the present study was to evaluate the effects of postoperative administration of intravenous amiodarone or magnesium sulphate in preventing AF and on postoperative recovery. In addition, variables predisposing to postoperative AF were assessed.

Methods

Patients scheduled for elective coronary bypass grafting (CABG) were allocated randomly in a double-blind, placebo-controlled study. The study protocol was approved by our institutional ethics committee and all patients gave written consent the day before surgery. Exclusion criteria

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were refusal of consent, chronic AF, second- or third-degree atrioventricular block, pacemaker dependence, amiodarone treatment in the year preceding the operation, thyroid disease, other associated heart surgery, valvular disease, chronic renal failure (defined as a creatinine clearance rate less than 30 ml min^{-1}) and liver dysfunction (prothrombin time <50% and/or bilirubin >35 μmol $litre^{-1}$ and/or the presence of ascites).

Preoperative and postoperative management

Before transfer to the operating room, all patients received premedication with diazepam and morphine, and chronic β-blocker therapy was replaced with metoprolol by mouth. General anaesthesia was induced and maintained with midazolam, fentanyl and pancuronium bromide, adjusted to body weight and elimination half-time. Systemic hypothermic (28°C) cardiopulmonary bypass (CPB; aortic and right atrium cannulation) associated with repeated cold cardioplegic-induced cardiac arrest was used. At the end of the surgical procedure, the patients were transferred to the ICU.

Weaning from mechanical ventilation and tracheal extubation were done as early as possible. Weaning from catecholamine infusion was guided by standard haemodynamic criteria. The pulmonary artery catheter was removed when there was no evidence of cardiac dysfunction and no need for catecholamine infusion. Patients were discharged from the ICU to the ward as soon as their haemodynamic and respiratory condition was stable.

Study design

The randomization procedure was accomplished by the Pharmacy Department using colour-coded spheres extracted from an opaque container. Additional patients were allocated to compensate for technical drop-outs. Patients were allocated to one of three groups, to receive a 72-h continuous intravenous infusion of amiodarone 900 mg per 24 h (Cordarone; Sanofi-Winthrop, Basel, Switzerland) or magnesium sulphate 4 g (16 mmol, 32 mEq) per 24 h (Bichsel, Interlaken, Switzerland) or placebo (0.9% NaCl), starting within 1 h of arrival in the ICU. The study drugs were prepared daily in an opaque syringe and tubing (Perfusor; Braun, Melsungen, Germany) by an independent observer. Throughout the 72-h infusion period, a Holter ECG recording (Cardiocorder three-channel recorder, model 459; Delmar Avionics, Irvine, California, USA) was obtained. Additional 12-lead ECGs were recorded every 12 h.

The primary end-point of the study was the prevention of AF. If AF occurred, the prophylaxis was considered to have failed and the study was terminated; the drug code was opened and the patient was treated as appropriate. The Holter ECG recording was analysed on completion of the 72-h study period or earlier if the study was terminated because of arrhythmia. Supraventricular arrhythmia episodes were then detected visually and printed for accurate diagnosis by two of the investigators. Considering the potential adverse effect of acute amiodarone infusion,[15] an intermediate safety analysis was planned after the inclusion of half of the patients.

Definitions of supraventricular arrhythmia

Supraventricular tachycardia was defined as an arrhythmia of more than three narrow QRS complexes at a rate greater than 100/b.p.m. and lasting more than 30 s. Atrial fibrillation was defined as totally irregular atrial rhythm leading to irregular ventricular rhythm.

Data collection

Relevant patient characteristics, associated medical conditions, concomitant treatment, pulmonary and renal function tests were recorded. Also recorded were perioperative variables, including aortic cross-clamping and CPB duration, the number and type of coronary bypasses performed, and treatment at weaning from CPB. After surgery, heart rate, mean arterial pressure, central venous pressure and, when available, mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index (triplicate normal saline injection at room temperature, thermodilution technique) and stroke volume index were recorded 6-hourly. Arterial blood gases and electrolytes (Na^+, K^+ and Ca^{2+}) were also measured at the same intervals. Total plasma magnesium concentrations were measured 12-hourly. Additional recorded variables included postoperative complications and drug-related side-effects. Data obtained from the Holter ECG recording were the number of isolated or paired supraventricular ectopic beats and the number of supraventricular tachycardia runs, with their ventricular response rate and the respective count of QRS complexes. To adjust for the variability in the number of beats per hour of the ECG Holter recordings, the number of abnormalities was normalized to 1000 recorded beats.

Statistical analysis

Continuous variables were expressed as mean (SD) unless otherwise specified. The two intervention groups were compared with placebo using the unpaired *t*-test when dealing with approximately normally distributed variables and the Mann–Whitney test otherwise. The χ^2 test was used for categorical variables. Kaplan–Meier analysis was used to analyse the delay in the onset and the duration of arrhythmia in the three groups. Potential predictors of the development of AF included patient characteristics, perioperative myocardial infarction and plasma magnesium concentration. Logistic regression was used to assess univariate associations between predictor variables and the onset of AF. All predictor variables that exhibited

Table 1 Baseline clinical characteristics (n=147). Values are mean (SD) unless indicated otherwise. LVEF, left ventricular ejection fraction; FEV$_1$/FVC, forced expiratory volume at 1 s/forced vital capacity; ACE, angiotensin converting enzyme

	Patient group		
	Amiodarone (n=49)	**Placebo (n=51)**	**Magnesium (n=47)**
Age (yr)	65 (44–78)	65 (37–88)	65 (46–81)
Sex (M/F)	43/6	43/8	42/5
Weight (kg)	78 (11)	76 (12)	76 (10)
Myocardial infarction <6 months (n)	9	9	3
Myocardial infarction >6 months (n)	20	14	15
History of supraventricular arrhythmias (n)	1	2	1
Hypertension (n)	24	17	19
Diabetes (n)	13	6	6
Creatinine clearance (ml min^{-1})	75 (20)	72 (23)	71 (20)
History of stroke (n)	1	2	2
Previous heart surgery (n)	2	4	3
LVEF (mean %)	58 (14)	57 (13)	62 (15)
Diseased vessels [median (range)]	3 (1–3)	3 (1–3)	3 (1–3)
FEV$_1$/FVC (% predicted)	92 (11)	95 (10)	91 (12)
Concomitant cardiac medication			
Nitrate derivatives (n)	45	41	40
β-Adrenergic blocker (n)	27	33	24
Calcium channel blocker (n)	12	15	16
Digoxin (n)	1	2	0
ACE inhibitor (n)	13	10	8
Diuretic (n)	9	4	4
Coronary bypass grafts [median (range)]	3 (1–5)	3 (1–5)	3 (1–5)
Duration of CPB (min)	157 (54)	148 (47)	140 (38)
Duration of aortic cross-clamping (min)	100 (39)	103 (39)	91 (26)

significant univariate associations with AF (P<0.05) were tested in multivariate models; the final model included only statistically significant predictors (at the P<0.05 level).

Sample size and power

The frequency of AF detected by Holter ECG monitoring after CABG surgery is about 40%.[16] From previous studies on AF prophylaxis after CABG surgery,[8 17 18] we expected a reduction of 50% in the occurrence of AF. Ninety-one patients per group would have been needed to detect such a difference with a power of 80% and α=5%. An interim analysis was planned after inclusion of 50 patients in each group.

Results

Study population

The first 155 patients meeting our inclusion criteria were studied over an 18-month period. During this period, 299 patients were admitted to our 20-bed surgical Intensive Care Unit after elective CABG. Six patients were excluded from the analysis because of early withdrawal due to haemodynamic instability [four in the amiodarone group: hypotension (1), major bradycardia (2), third-degree atrioventricular block (1); one in the magnesium group (cardiac arrest) and one in the placebo group (pacemaker dependence); P=0.2 between groups)]; two additional patients (one in the placebo and one in the magnesium group) were excluded because of incomplete data availability due to technical failure of the Holter ECG recording. The final number of patients included in the interim data analysis was 147 (amiodarone 49, magnesium 47, placebo 51).

The mean age of evaluable patients was 65 yr (range 37–88). The three groups were similar in baseline characteristics and surgical procedure (Table 1). Variables recorded on arrival at the ICU, including haemodynamics, laboratory and electrocardiograph findings, were similar among the three groups (data not shown).

Tachyarrhythmias

The frequency of AF longer than 30 s was 27% in the placebo group, 14% in the amiodarone group (P=0.14) and 23% in the magnesium group (P=0.82) (Table 2). The time to onset of AF after the start of the prophylactic infusion is illustrated in Figure 1 (log-rank test: amiodarone versus placebo P=0.17, magnesium versus placebo P=0.5). Among patients who developed AF, its onset was significantly delayed in the amiodarone group compared with the placebo group (Table 2).

Predictors of postoperative arrhythmia

The univariate analysis identified the following six variables that were positively associated with the subsequent onset of postoperative atrial fibrillation at the level of P<0.05: age; history of supraventricular tachycardia; creatinine clearance; perioperative myocardial infarction; duration of pulmonary artery catheter monitoring; and plasma magnesium concentration 24 h after the operation <0.9 mmol litre^{-1}. From the multivariate logistic regression model,

Table 2 Occurrence and number of episodes of atrial fibrillation. *Difference between amiodarone and placebo. †Difference between magnesium and placebo HR, heart rate

	Patient group				
	Amiodarone (n=49)	***P******	**Placebo (n=51)**	***P*†**	**Magnesium (n=47)**
AF					
Occurrence [n (%)]	7 (14%)	0.14	14 (27%)	0.82	11 (23%)
Delay in onset after start of infusion [h; mean (SD)]	54 (10)	0.02	42 (12)	0.37	45 (14)
Episodes [n (max number of episodes/patient)]	11 (5)	0.28	14 (1)	0.88	17 (3)
HR during AF [b p m., mean (SD)]	140 (18)	0.12	153 (18)	0.26	146 (9)

independent predictors were older age (OR=1.9 for every 10 yr) and plasma magnesium concentration <0.9 mmol litre^{-1} 24 h after the operation (OR=6.7). This model classified correctly 82% of all observations.

Postoperative course

Haemodynamics, blood gas and electrolytes

No differences in haemodynamic values were found compared with placebo, except that patients receiving intravenous amiodarone had slower heart rates from 18 h after starting the infusion (Fig. 2). No differences were observed in pH, Pa_{CO_2} and Pa_{O_2}, or in blood concentrations of potassium and ionized calcium. In the magnesium group, higher plasma magnesium levels compared with baseline and the placebo group (P<0.01) were detected 12 h after starting the infusion and thereafter.

Postoperative complications

The incidences of myocardial infarction, cardiac arrest, requirement for surgical haemostasis and prolonged tracheal intubation (>72 h) were similar among the three groups. The occurrence of AF was not associated with attributable morbidity.

Compared with the placebo group, patients in the amiodarone group required a longer period of catecholamine infusion [placebo 19 (13), amiodarone 32 (18) h; P<0.01] and concomitant invasive monitoring with an indwelling pulmonary artery catheter [placebo 31 (14) h, amiodarone 42 (16) h; P<0.01]. In the magnesium group, neither the duration of catecholamine infusion [10 (11) h, not significant] nor the duration of invasive monitoring [31 (10) h, not significant] was different from the values for the placebo group.

The length of stay in the ICU was significantly longer in patients receiving amiodarone (median 4 days, range 2–9 days) than in the placebo group (3, 2–7 days; P<0.05). The median length of stay in the ICU in the magnesium group was 3 days (2–21). In the placebo group, patients with sustained AF stayed longer in the ICU (5, 4–7 days) than patients maintaining a sinus rhythm (3, 2–6 days; P<0.05).

One patient in the amiodarone group died 3 days after surgery from acute myocardial infarction and cardiogenic shock and a patient in the placebo group died 5 days after surgery.

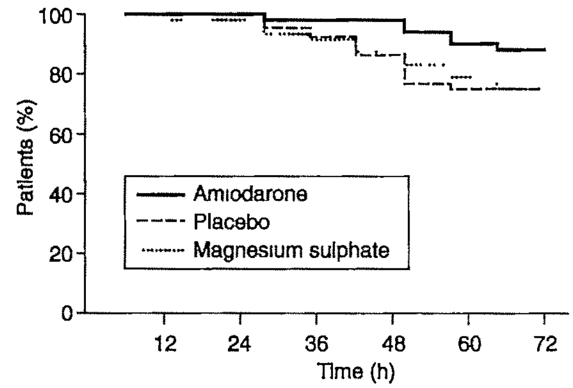

Fig 1 Percentage of patients without AF and delay in AF onset in patients receiving intravenous amiodarone, placebo or magnesium sulphate.

Discussion

The interim analysis did not demonstrate the effectiveness of either amiodarone or magnesium for the prophylaxis against postoperative AF. Although amiodarone halved the rate of occurrence of AF, as shown previously.[10] it was associated with a longer need for catecholamine infusion and invasive monitoring and a longer stay in the ICU. The adverse haemodynamic effect seen in our series has already been described.[19] Concerning the longer ICU stay observed in the amiodarone group, if we extrapolate to 1000 post-CABG patients, AF will prolong ICU stay by 2 days per patient, and an occurrence of 27% will result in 540 AF-attributable ICU patient days. Prophylaxis with amiodarone will increase ICU stay by 1000 patient days, whereas the avoidable risk of AF of 13% will reduce the ICU stay by only 260 days. Thus, the avoidance of prophylaxis will save 740 patient days in the ICU. In addition, patients in the amiodarone group experienced a slightly higher rate of adverse events, which may have been attributable to the study drug; these events included hypotension, atrioventricular block and bradycardia, and led to study termination in four of the patients. Intravenous magnesium did not reduce the occurrence of AF. On the basis of the present intermediate analysis, we judged it futile to proceed with further patient recruitment, because there was no evidence of effectiveness from prophylaxis in patients undergoing

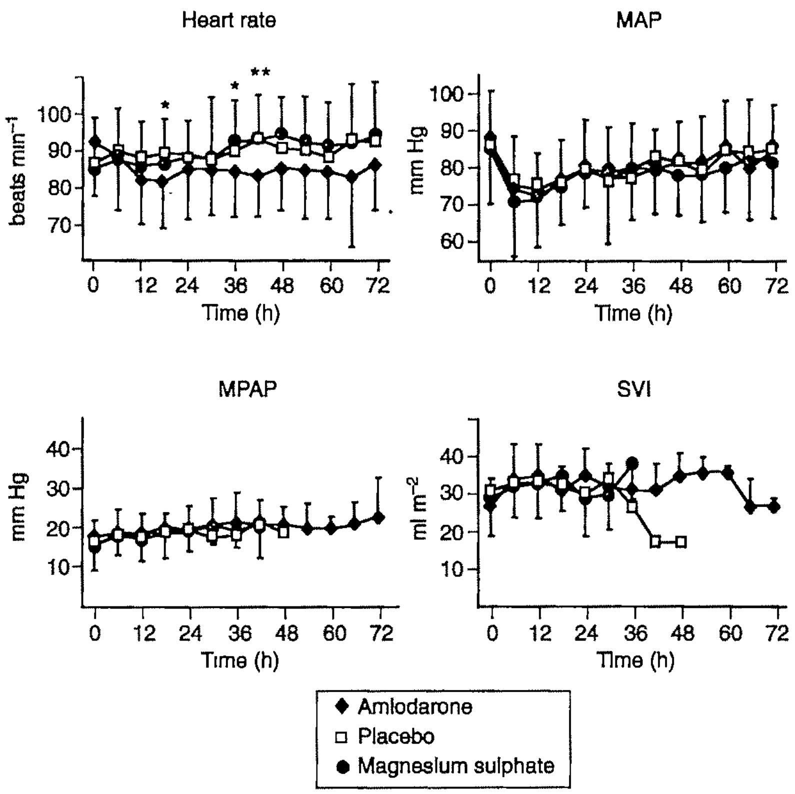

Fig 2 Six-hourly postoperative time course of heart rate, mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP) and stroke volume index (SVI) in patients receiving intravenous amiodarone, placebo or magnesium sulphate. *$P<0.05$, amiodarone versus placebo.

elective CABG surgery and no additional morbidity attributable to the occurrence of AF.

Prophylaxis against AF in cardiac surgery may still be indicated in selected populations such as patients presenting with valvular disease, which is complicated by a higher incidence of AF. Furthermore, as shown in our study, older patients are at higher risk of developing AF and may also benefit from prophylaxis.

The relevance of the delayed onset of AF with amiodarone remains questionable.

In our study, as shown by England and colleagues,[20] although magnesium sulphate prophylaxis was ineffective in preventing AF, patients presenting with plasma magnesium levels higher than 0.95 mmol litre^{-1} were protected from the development of AF. Variables predictive of postoperative AF onset were older age, and plasma magnesium concentrations in the low normal range (<0.95 mmol litre^{-1}) regardless of replacement therapy. Previous retrospective and observational studies emphasized the importance of age as an important independent predictor of AF after CABG.[21–24] Other predictors were chronic obstructive pulmonary disease, right coronary artery stenosis, preoperative β-adrenergic blockers and digoxin and chronic renal failure.[21–24] Among the variables we studied, our results confirm the increased risk associated with older age, with a 2-fold increase for each 10-yr interval.

In conclusion, perioperative administration of amiodarone intravenously required prolonged vasoactive and inotropic support, longer invasive monitoring and a longer stay in the ICU. The decision to administer amiodarone prophylaxis should be made cautiously, taking account of the increased risks of arrhythmia associated with, for example, age and mitral valve surgery, and the side-effects associated with this drug. Postoperative magnesium supplementation was ineffective in reducing the occurrence of AF.

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Giving long-persistent starch as volume replacement can cause pruritus after cardiac surgery

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We reviewed the prevalence and severity of pruritus in 85 patients after cardiac surgery. EloHAES, a long-lasting hydroxyethylated starch, was given to 59 of these patients. None of the patients who did not receive EloHAES developed pruritus, compared with 22% of those who did (*P*=0.007). The timing of onset, duration and severity of the pruritus are similar to those found previously for other hydroxyethylated starches, and the cause of this pruritus is likely to be similar. Hydroxyethyl starch can cause long-term pruritus.

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There is continued interest in the types of intravenous fluid that are most appropriate for particular clinical indications. These fluids include crystalloids, plasma, albumin and the synthetic colloids, which include gelatin derivatives, dextran solutions and hydroxyethylated starches.

Many studies have compared different colloids. The variables most often assessed include maintenance of intravascular volume, cardiac function, coagulation variables[1–3] and end-organ function.[4] No one colloid has a clinical advantage, despite theoretical and *in vitro* advantages of one agent over another. Hydroxyethyl starch remains in the intravascular compartment for longer, so it is believed to cause less tissue oedema than other colloids. Some suggest that hydroxyethyl starch molecules can 'plug' leaky capillaries[4] and prevent fluid moving from the vessels to the tissues.

Giving hydroxyethyl starch may cause significant and prolonged pruritus.[5] We assessed the prevalence and severity of pruritus in patients who had received EloHAES (hydroxyethyl starch 200/0.62) for volume replacement during cardiac surgery, compared with cardiac surgical patients who had not.

Patients and methods

Over a 9 week period, we reviewed 85 consecutive, unselected patients who had had cardiac revascularization or heart valve surgery within the previous year. This time period was chosen arbitrarily to allow good memory recall. A single unblinded observer carried out a structured interview according to a standard proforma (Fig. 1). Of the patients interviewed, 58 patients received EloHAES as part of their fluid management during or after surgery, and 27 patients received no hydroxyethyl starch. Other fluids used included 0.9% saline, Gelofusine and blood products as indicated clinically. The decision to administer starches to these patients was made by individual anaesthetists on the basis of their apparent relative merits. Case numbers and case mix were similar between anaesthetists. The numbers in each group reflected the number of anaesthetists who administered starches.

Pruritus was classified as mild, moderate or severe according to the following criteria: mild, present several times a week, but did not interfere with the patient's daily routine; moderate, present every day and sometimes interfered with the daily routine; severe, was present every day, interfered with the daily routine and was of sufficient intensity for the patient to seek medical help. The onset, duration, aggravating and relieving factors, site of pruritus and the volume of EloHAES administered were also recorded.

Statistical analyses were performed using the SPSS 8.0 for Windows statistical package. The presence or absence of pruritus in individuals who had received EloHAES was compared with that in the control population using 2 × 2 contingency tables. Fischer's exact test was performed, as the expected numbers were too small for χ^2 results to be accurate. The volume of EloHAES administered was compared between patients with and without pruritus, and then in patients with no, mild, moderate and severe pruritus,

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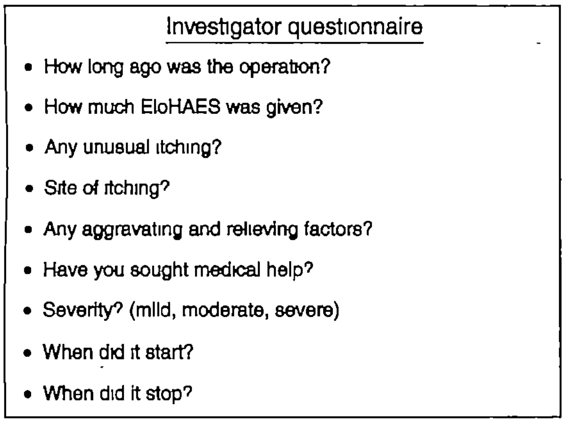

Investigator questionnaire

- How long ago was the operation?
- How much EloHAES was given?
- Any unusual itching?
- Site of itching?
- Any aggravating and relieving factors?
- Have you sought medical help?
- Severity? (mild, moderate, severe)
- When did it start?
- When did it stop?

Fig 1 Proforma of questions put to patients in the structured interview.

Table 1 Frequency and severity of pruritus in EloHAES and control groups

	Number (%) of patients	
Pruritus	**EloHAES**	**Control**
None	45 (78)	27 (100)
Mild	7 (12)	0
Moderate	0	0
Severe	6 (10)	0

Table 2 Volumes of EloHAES administered for each grade of pruritus

Pruritus	Volume in litres of EloHAES infused (g)	
	Median	**Range**
None	1.35 (81)	0.5–2 (30–120)
Mild	1.4 (84)	0.5–2.5 (30–150)
Severe	1.5 (90)	1–2.4 (60–144)

using the Mann–Whitney *U*-test and Kruskal–Wallis tests, respectively. Two-tailed *P* values of <0.05 were considered statistically significant.

Results

No patients experienced pruritus in the group who did not receive any EloHAES, compared with 22% in the EloHAES group (P=0.007). Pruritus was classed as mild in 54% and severe in 46% (Table 1). The mean (range) volume of EloHAES administered was as follows: no pruritus, 1.35 (0.5–2) litres; mild pruritus, 1.4 (0.5–2.5) litres; severe pruritus, 1.5 (1–2.4) litres (Table 2). There was no statistically significant difference between these groups, but a trend to greater volume given to the severely pruritic group was noticed. The median (range) onset of pruritus in the EloHAES group was 4 (1–12) weeks. Pruritus was still present in 77% of those affected at the time of interview; the greatest duration was ≥9 months. The site of pruritus varied: 40% of patients experienced pruritus in the natal cleft, 30% on the lower back and 20% on the upper back. Other sites included the neck, feet, hands, chest and abdomen. There were no consistent aggravating or relieving factors.

Discussion

We found that volume replacement with EloHAES in patients undergoing cardiac surgery was associated with pruritus.

Pruritus after administration of hydroxyethyl starch was first reported in a patient undergoing leucophoresis.[5] Subsequent reports have demonstrated an association between various hydroxyethyl starches and pruritus. The clinical features vary and skin changes are often absent. The pruritus may be generalized or localized, have a delayed onset of up to several weeks; it may have precipitating factors such as warmth and mechanical irritation.[6–9] The pruritus is frequently persistent, lasting months or even years,[10] and is usually refractory to treatment with antihistamines or steroids, although some benefit has been reported with capsaicin,[11] hydroxyzine[9 12 13] and amantidine.[14]

Hydroxyethyl starches have hydroxyethyl groups bound to a high molecular weight amylopectin backbone, which delays rapid hydrolysis by plasma α-amylase. The main difference between the different hydroxyethyl starch products is in their molecular weights and in the level of substitution with hydroxyethyl groups. The latter is now thought to be the major determinant of pharmacological behaviour.[15 16] EloHAES is a medium molecular weight hydroxyethyl starch, with a mean molecular weight of 200 000 Da (80% between 13 700 and 500 000), and has a molar substitution of 0.62, that is every 100 glucose moieties have 62 hydroxyethyl groups attached. The low molecular weight molecules and breakdown products are excreted in the urine, so hydroxyethyl starch solutions are contraindicated in severe chronic renal insufficiency. Hydroxyethyl starches are deposited in various tissues and delayed excretion occurs following metabolism by tissue glucosidases.[17–25] Skin biopsies from individuals who developed pruritus have shown deposits of hydroxyethyl starch within the intracellular vacuoles of macrophages, Langerhans cells, keratinocytes, vascular endothelium, perineural cells and sweat gland epithelia.[6 26] The size and severity of the deposits may depend on the dose and preparation administered.[10] Symptomatic improvement can occur as hydroxyethyl starch deposits diminish in size, which may take ≤3 years.[6]

A correlation between the volume of hydroxyethyl starch infused and the severity of pruritus has been found.[6 10 21 26 27] In one study, the mean dose of hydroxyethyl starch in the group suffering from pruritus was 7.8 g kg^{-1}, equivalent to 9.75 litres of EloHAES, compared with 1 litre equivalent in the non-pruritic group.[21] Individuals given 150 g of hydroxyethyl starch in another study had a 1% incidence of pruritus, which increased by

5.5% with each additional 50 g dose.[26] The incidence of pruritus associated with Pentastarch in an intensive care population[28] was slightly higher than that found in the present study. This was possibly because a greater volume of starch was administered. A similar proportion also suffered severe pruritus, although not defined, with a comparable duration to our study. We were unable to demonstrate a correlation between dose and response in our study, either because we used less starch, or because the smaller range of doses administered may not have had sufficient power to detect a correlation. One study failed to demonstrate an increase in pruritus in a group receiving hydroxyethyl starch when compared with a group receiving lactated Ringer's solution.[29] The volumes of hydroxyethyl starch in that study were much smaller (around 650 ml in total) than those in other studies where pruritus was found, suggesting that there may be a 'threshold dose' for pruritus to occur. Cox and Popple suggested that metabolic polymorphism could be responsible for abnormal handling of hydroxyethyl starches, thus predisposing certain patients to larger tissue deposits of hydroxyethyl starch.[7] This could help to explain why in our study some patients developed pruritus and others did not, despite similar volumes of starch administered.

We found that 22% of cardiac surgical patients who received EloHAES suffered from pruritus, often with sufficient severity to interfere with their daily routine. Our findings support previous work that has linked administration of other hydroxyethyl starches with pruritus. As EloHAES contains the same basic molecular structure as other hydroxyethyl starch solutions, we propose that the mechanism of pruritus is similar.[10 27] Many hydroxyethyl starches can cause long-term pruritus, and this should be considered in the choice of volume replacement therapy.

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Reduction in standard MAC and MAC for intubation after clonidine premedication in children

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We examined the relative effects of different doses of oral clonidine on the MAC for endotracheal intubation (MAC_{EI}) and the MAC for skin incision (MAC) in children. We studied 90 children (15 in each group) (age range 2–8 yr, weight 10–27 kg, height 89–124 cm) who received one of three preanaesthetic medications: placebo (control), oral clonidine 2 $\mu g\ kg^{-1}$, or oral clonidine 4 $\mu g\ kg^{-1}$ 100 min before anaesthesia. Anaesthesia was induced and maintained with sevoflurane in oxygen and air without i.v. anesthetics and neuromuscular relaxants. The end-tidal sevoflurane concentration was kept constant for ≥15 min before tracheal intubation or skin incision. MACs were determined using Dixon's 'up-and-down method'. Mean (SD) MAC_{EI}s of sevoflurane were 2.9 (0.1) %, 2.5 (0.1) % and 1.9 (0.1) % ($P<0.05$), and MACs were 2.3 (0.1) %, 1.8 (0.1) % and 1.3 (0.1) % ($P<0.05$), respectively, in control, clonidine 2 $\mu g\ kg^{-1}$ and clonidine 4 $\mu g\ kg^{-1}$ groups. The MAC_{EI}s and MACs decreased dose-dependently. The MAC_{EI}/MAC ratio (1.4) was not affected by clonidine.

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Clonidine, an α_2-adrenergic agonist, has recently been used as a preanaesthetic medication for children,[1] and decreases the minimum alveolar concentration (MAC) in animal experiments.[2 3] The MAC for endotracheal intubation (MAC_{EI}) is the end-tidal concentration of volatile anaesthetics at which a smooth tracheal intubation is possible in 50% of patients.[4] The MAC_{EI}/MAC ratio has been determined for several halogenated anaesthetics (halothane,[4] enflurane[5] and sevoflurane[6 7]). The ratio for sevoflurane is approximately 1.3 in children[6] and 3 in adults.[7] The effects of different doses of clonidine on the MAC_{EI}/MAC ratio have not been fully elucidated in children.[8]

To study this interaction, we conducted a randomized, single-blind comparison of MAC_{EI}/MAC ratios for sevoflurane in children receiving a placebo, or clonidine 2 or 4 $\mu g\ kg^{-1}$ premedication.

Methods

Patient selection

We studied 90 children, ASA physical status I, ranging in age from 2 to 8 yr, and scheduled for general anaesthesia for elective repair of inguinal hernia under general anaesthesia. The study was approved by our Clinical Investigation Committee, and informed consent was obtained from the parent or guardian of each patient. Patients with airway malformation, clinical evidence of a difficult airway, asthma or any sign of upper respiratory infection on preoperative examination were excluded from the study. Patients taking sedatives, antihistamines, central nervous system (CNS) depressants or anti-seizure medication, or who had CNS disorders including spinal cord dysfunction were also excluded from the study.

General procedure

Patients fasted for a minimum of 5 h before induction of anaesthesia. An i.v. infusion of 2% dextrose in lactated Ringer's solution at a rate of 6 ml $kg^{-1}\ h^{-1}$ was started. A precordial stethoscope was used to monitor heart and breath sounds. The patients were monitored with an electrocardiogram, a pulse oximeter and by measuring indirect arterial pressure. Throughout the study the inspired and end-tidal concentrations of agents were measured with a gas monitor (AS/3; Datex, Helsinki, Finland) which was calibrated

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before each use. Before tracheal intubation with a noncuffed, appropriately sized tube, the end-tidal concentrations of agents were measured at the nose via a cannula; after intubation, they were measured from the distal end of the tracheal tube using a cannula that had been inserted through the elbow of the circuit so that its tip was within 1 cm the tip of the tracheal tube. Accuracy of end-tidal measurements was maximized by confirming the return of the end-tidal carbon dioxide trace to zero and a plateau of the exhaled concentration values.

The patients were randomly allocated to one of six groups (15 patients per group) using computer-generated numbers. The patients received one of three premedications (two groups for each premedication): placebo (control), oral clonidine 2 μg kg^{-1}, or oral clonidine 4 μg kg^{-1} 100 min before anaesthesia. Anaesthesia was induced with 5% sevoflurane in oxygen without intravenous anaesthetics and neuromuscular relaxants. The end-tidal sevoflurane concentrations and intervals used in MAC and MAC_{EI} determination were chosen from a pilot study.

Experimental protocol

Measurement of MAC_{EI}

Initially spontaneous respiration was assisted, and then respiration was controlled manually. When the end-tidal sevoflurane concentration reached a predetermined value, then end-tidal concentration was kept constant for ≥15 min before tracheal intubation. Laryngoscopy and tracheal intubation were attempted quickly using a curved laryngoscope and an uncuffed tracheal tube without neuromuscular relaxants or adjuvants. Each concentration at which laryngoscopy and tracheal intubation were attempted was chosen according to the modification of Dixon's 'up-and-down' method[9] with 0.25% as a step size (2.5%, 2.75%, 3.0% and 3.25% in the control group; 2.25%, 2.5% and 2.75% in the clonidine 2 μg kg^{-1} group, and 1.75%, 2.0% and 2.25% in the clonidine 4 μg kg^{-1}group). A single measurement was obtained per patient. When tracheal intubation was accomplished without gross purposeful muscular movements, it was considered smooth. Coughing and bucking were considered purposeful. Patients who moved during laryngoscopy or after tracheal intubation were immediately given 4–5% sevoflurane. They were regarded as not having been intubated smoothly. A single anaesthesiologist performed all tracheal intubations.

Time for tracheal intubation was defined as the time between discontinuation of face-mask ventilation and connection of the endotracheal tube to the anaesthesia circuit.

Measurement of MAC

Tracheal intubation was facilitated with 5% sevoflurane in oxygen without i.v. anaesthetics and neuromuscular relaxants, then anaesthesia was maintained with sevoflurane in oxygen and air. The lungs were mechanically ventilated using a volume-cycled ventilator. After the end-tidal sevoflurane concentration had reached a predetermined value, the concentration was maintained for at least 15 min before skin incision. Before skin incision, we recorded end-tidal sevoflurane for calculation. After skin incision, the patients were observed for ≥1 min for gross purposeful muscular movements. Coughing, bucking and straining were not considered purposeful. Patients who showed purposeful muscular movements during and/or after skin incision were immediately given 4–5% sevoflurane. Each concentration at which skin incision was attempted was predetermined according to the modification of Dixon's 'up-and-down' method[9] (2.0%, 2.25%, 2.5% and 2.75% in the control group; 1.5%, 1.75% and 2.0% in the clonidine 2 μg kg^{-1} group, and 1.0%, 1.25% and 1.5% in the clonidine 4 μg kg^{-1} group).

Absence of any purposeful movements was determined by a single anaesthesiologist who was blinded to the tested sevoflurane concentration and whether clonidine was given or not. End-tidal concentration of carbon dioxide was maintained at 4.7–5.1 kPa during the study, while rectal temperature was maintained at 36–37°C.

Data analysis

We determined MAC_{EI} and MAC by calculating the midpoint concentration of all independent pairs of patients involving a crossover (i.e. movement or no movement). MAC_{EI} or MAC was defined as the average of the crossover midpoints in each crossover subgroup. In addition, the standard deviation of MAC_{EI} or MAC was the standard deviation of the crossover midpoint in each group Patient characteristics and pre-anaesthetic oral clonidine doses are expressed as mean (SD). Statistical comparisons among the three premedication groups (control, clonidine 2 μg kg^{-1} and clonidine 4 μg kg^{-1}) were performed using ANOVA with Fisher's least significant difference test for *post hoc* analysis (Stat View software, SAS Institute Inc., NC, USA and a Macintosh computer). Statistical comparisons between the same premedication groups were performed using two-factor factorial ANOVA with Fisher's least significant difference test for *post hoc* analysis. In all cases, $P<0.05$ was considered the minimum level of statistical significance.

Results

The characteristics of each group were very similar. The mean (SD) age was 5 (2) yr in each group. The mean weight was between 18 and 20 kg, and the mean height was between 107 and 108 cm in the six groups.

Figures 1 and 2 show the MAC_{EI} and MAC, respectively, for each each patient in the control (A), clonidine 2 μg kg^{-1} (B) and 4 μg kg^{-1} clonidine (C) groups, each measurement being represented with a circle. The MAC_{EI}s and MACs determined with the up-and-down method decreased dose-

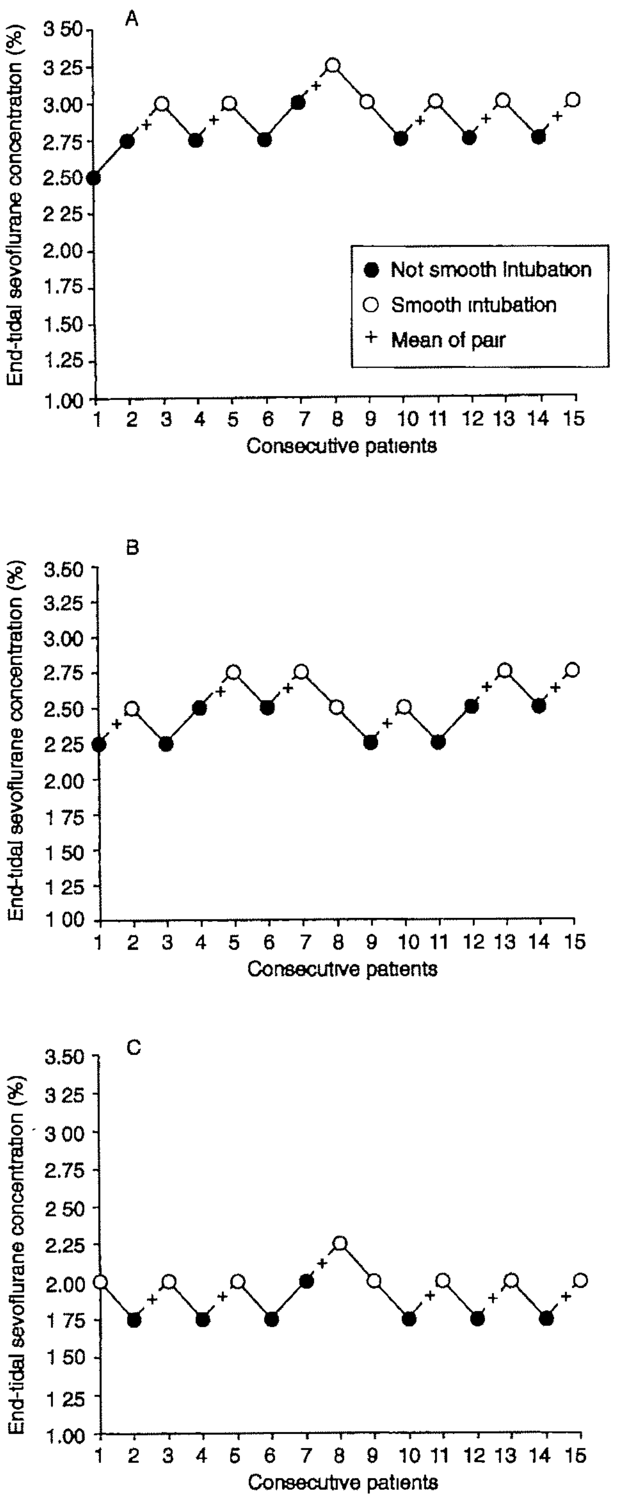

Fig 1 End-tidal sevoflurane concentration and the responses of consecutive patients (15 in each group) in whom endotracheal intubation was attempted. Each patient's data are represented with a circle, mean (SD) $\mathrm{MAC_{EI}}$s at which smooth endotracheal intubation was possible in 50% of patients were 2.9 (0 1) %, 2.5 (0.1) % and 1 9 (0.1) %, in control (A), clonidine 2 μg kg^{-1} (B) and clonidine 4 μg kg^{-1} (C) groups, respectively.

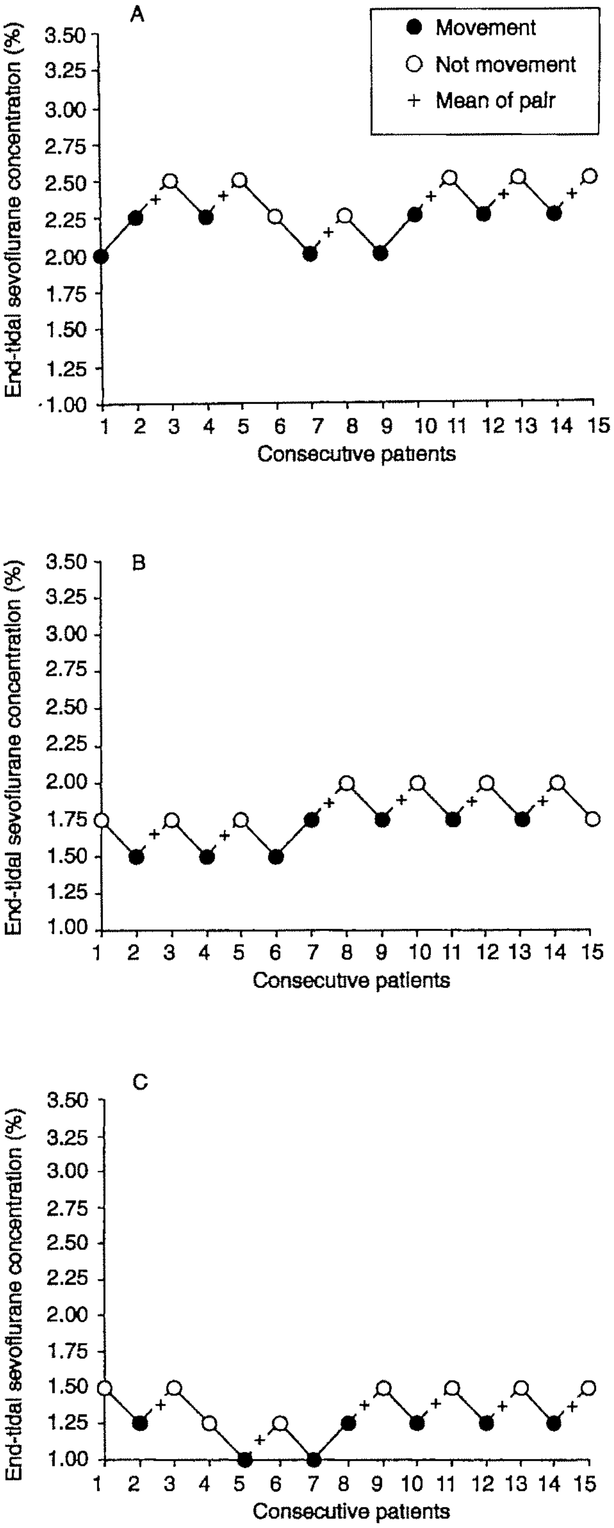

Fig 2 End-tidal sevoflurane concentration and the responses of consecutive patients (15 per group) in whom skin incision was attempted. Each patient's data are represented with a circle. The mean (SD) MACs at which skin incision was possible in 50% of patients were 2.3 (0 1) %, 1.8 (0.1) % and 1.3 (0.1) % in control (A), clonidine 2 μg kg^{-1} (B) and clonidine 4 μg kg^{-1} (C) groups, respectively.

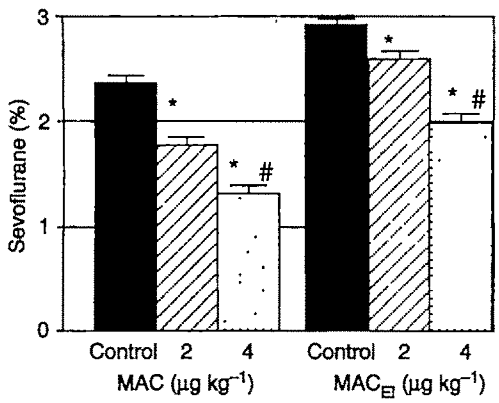

Fig 3 The MAC_{EI}s and MACs determined with the up-and-down method decreased dose-dependently. The MAC_{EI}/MAC ratio was 1.4 in all groups. Values are mean (SD). *$P<0.05$ *vs* control, #$P<0.05$ *vs* clonidine 2 $\mu g\ kg^{-1}$ group.

dependently ($P<0.05$) (Fig. 3). The MAC_{EI} was greater than the MAC for each clonidine dose ($P<0.05$). Time for tracheal intubation did not exceed 10 s. No patients had dysrhythmia, bradycardia or hypotension that necessitated treatment during the study.

The MAC_{EI}/MAC ratio (1.4) was unaffected by clonidine premedication.

Discussion

We set out to determine the effect of oral clonidine preanaesthetic medication on the MAC_{EI}/MAC ratio in children. We compared MAC_{EI}/MAC ratios for sevoflurane in children receiving clonidine 2 or 4 $\mu g\ kg^{-1}$ or a placebo. We observed a similar reduction in end-tidal sevoflurane concentrations for the two different endpoints: loss of response to tracheal intubation and loss of response to skin incision. We found in a previous study that oral clonidine 4.4 $\mu g\ kg^{-1}$ decreased MAC.[10] Our current findings that oral clonidine 4 $\mu g\ kg^{-1}$ decreased MAC and MAC_{EI} by 43% and 35%, respectively, support our previous studies. α2-Adrenergic agonists have an analgesic effect, involving both supra-spinal and spinal sites.[11, 12] A selective α2-adrenergic agonist, dexmedetomidine, has been shown in animal studies to decrease the MAC for halothane so much that it may act as an anaesthetic by itself at high doses.[13]

We previously reported that the MAC_{EI} and MAC_{EI}/MAC ratio for sevoflurane were 2.69% and 1.3, respectively, in children.[6] The MAC_{EI}/MAC ratio for other volatile anaesthetics, halothane[4] and enflurane, [5] has been shown to be 1.3. In the present study, we found that the MAC_{EI}/MAC ratio was approximately 1.4 at each clonidine dose (0, 2 or 4 $\mu g\ kg^{-1}$). This relationship seems to be maintained in patients receiving oral clonidine premedication.

In a study of rabbits given clonidine 50 $\mu g\ kg^{-1}$ daily for 3 days, the MAC for halothane decreased by 16%.[2] In rats given intraperitoneal clonidine (10–1000 $\mu g\ kg^{-1}$), the MAC for halothane was reduced by 32–42%.[14] We found that oral clonidine 4 $\mu g\ kg^{-1}$ reduced the MAC or MAC_{EI} for sevoflurane by 43% or 34%, respectively, in this study. These findings suggest that clonidine, in doses clinically used, reduces the MACs of volatile anesthetics by no more than 45%.

It has been reported that the MAC for sevoflurane in children is approximately 2.5%.[15, 16] In the present study, we found a similar MAC (2.33% in the placebo group), which was slightly higher than a value previously reported by us (2%).[6] The difference in MACs between studies may be explained in part by the step size used in MAC determination (0.25% in the present study and 0.5% in our previous one). The fact that the MAC_{EI} value in the present study (2.92% in the placebo group) was slightly greater than our previous reported value (2.7%)[6] may also partly depend on the step size used in MAC_{EI} determination (0.25% in the present study and 0.5% in our previous one). Further investigation is required to explain these differences fully. We determined the end-tidal sevoflurane concentrations and intervals from a pilot study, and used 0.25% as a step size in order to obtain precise values in this study.

Because the elimination half-life of clonidine ranges from 6 to 24 h, with a mean of about 12 h,[17] clonidine is likely to remain effective over the time of the study, and changes in the effect of clonidine are unlikely to alter determination of MAC_{EI} and MAC.

In conclusion, clonidine reduced MAC_{EI} and MAC in a dose-dependent way. The MAC_{EI}/MAC ratio was unaffected by clonidine premedication, being 1.4 in each group.

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Effect of tramadol on electroencephalographic and auditory-evoked response variables during light anaesthesia

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Tramadol is a centrally acting opioid-like analgesic commonly used for analgesia during surgery. It has been stated that the use of tramadol increases the risk of awareness during anaesthesia. We studied 29 patients under steady state anaesthesia, ventilated via a laryngeal mask airway with 0.6 MAC isoflurane in 50% nitrous oxide, and with no surgical stimulus. The electroencephalogram (EEG) and auditory-evoked response (AER) were recorded throughout the study period, as were pulse and arterial pressure. Patients were given randomly a bolus of either saline (S), tramadol 100 mg (T1), or tramadol 200 mg (T2). Significant increases in systolic arterial pressure and decreases in heart rate were seen in the tramadol groups compared to the saline group. Significant, dose-related activation in all EEG variables (median power frequency, spectral edge, Delta Power and Alpha/Delta ratio) but no significant change in Pa or Nb amplitudes or latencies were noted. The EEG changes were not at levels thought to be associated with awareness. This study indicates that tramadol, whilst causing EEG activation, has no effect on depth of anaesthesia as measured by the AER.

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Keywords: analgesics non-opioid, tramadol; brain, electroencephalograph; brain, evoked potentials

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Tramadol is a centrally acting opioid agonist which, it has been suggested, increases the risk of awareness when used during anaesthesia.[1–3] Indeed, the British National Formulary[4] states that it is not recommended during light anaesthesia for this reason, and an editorial in the *British Journal of Anaesthesia*[1] described the perceived risk of tramadol-related awareness as '... a major drawback'. A recent study by Coetzee and colleagues[2] showed that tramadol caused significant dose-dependant activation of some electroencephalograph (EEG) variables when given as a bolus, although no patients recalled perioperative events or moved on skin incision. Lehmann and colleagues[3] have reported an increased incidence of awareness associated with perioperative tramadol usage.

The auditory-evoked response (AER) is a validated measure of depth of anaesthesia, especially amplitude and latency changes in the waves Pa and Nb.[5] An advantage that evoked responses have over raw or processed EEG data in measuring depth of anaesthesia is that they represent a measure of central nervous system responsiveness rather than a measure of its resting state. We decided to look for any changes in depth of anaesthesia reflected in the EEG and AER using patients undergoing steady state anaesthesia in response to a bolus dose of tramadol.

Patients and methods

The study was approved by Harrow Ethics committee, and written consent was obtained from each subject. Twenty-nine ASA I/II unpremedicated patients attending our hospital for routine surgery were recruited for the study.

On arrival in the anaesthetic room i.v. access was secured and standard monitoring commenced. Anaesthesia was induced with propofol 2 mg kg^{-1} and neuromuscular blockade obtained with vecuronium 0.1 mg kg^{-1}. A laryngeal mask airway was inserted, and the subjects' lungs were ventilated to an end tidal carbon dioxide level of 4.0–4.5 kPa. Anaesthesia was maintained with 50% nitrous oxide in oxygen and 0.6 MAC isoflurane (age adjusted).

After 20 min of stable anaesthesia with supplemental doses of vecuronium 0.05 mg kg^{-1} given as required, the subjects were allocated randomly by draw to one of three groups: an i.v. bolus of tramadol 100 mg or 200 mg (groups T1 and T2), or of saline (group S). The investigator was

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blinded to the group allocation and drug given during data collection and analysis. All haemodynamic and gas analysis variables were recorded at 5-min intervals. Fifteen minutes after drug injection, analysis was discontinued and the subjects were transferred to the operating theatre.

Data collection and analysis

The EEG signal was recorded via silver–silver chloride electrodes attached to the mastoid and forehead and stored on a PC-based system developed at Northwick Park Hospital.[6] The auditory stimulus for the AER was a rarefaction click delivered to the ears via tightly fitting earpieces at a rate of 6 s^{-1}, at 75 dB above the average hearing threshold. For EEG variables the digitized data were analysed using a fast Fourier transformation, and values for Median Frequency (F50), Spectral Edge (F95), Delta Power (DP) and Alpha/Delta ratio (A/D) generated. The EEG signal was analogue filtered at bandwidths of 25–500 Hz to produce the AER recording.

Although the AER was recorded throughout the study, averaged responses to clicks representing 1024 sweeps (2 min, 40 s) of EEG data were analysed corresponding to the period immediately before, and at 5, 10 and 15 min after the injection of saline or tramadol. Pa amplitude (Paa) and latency (Pal), and Nb amplitude (Nba) and latency (Nbl) were measured from printouts of these AER waveforms by an investigator, who was blinded to the drug or dose given. These variables were log transformed and analysis of variance was performed, looking for significant changes in each variable pre- to post-drug injection and, if these were present, whether this effect was dose related. A probability value $P<0.05$ was taken as significant.

Table 1 Subject characteristics by group

	Group S	Group T1	Group T2
Number of subjects	9	10	10
Age (years, median, range)	39, 18–62	45, 18–63	41, 24–60
Sex (male female)	4.5	4:6	5:5
Weight (kg, median, range)	69, 54–88	65, 51–97	73, 59–94

Results

Patient data are displayed in Table 1: the groups were similar in terms of age, sex and weight. No patients had explicit recall of events under anaesthesia.

Table 2 Mean baseline values for haemodynamic, EEG and AER variables by treatment group and the mean percentage change after drug injection. Significant changes pre- to post-dose are marked: #$P<0.05$; *$P<0.001$

Variable	Group	Mean value at baseline	Percentage change from baseline	
			Mean	95% CI
Heart rate	Saline (S)	65	–3	–5 to 0
(beats min^{-1})	Tramadol 100 mg (T1)	63	–10*	–12 to –7
	Tramadol 200 mg (T2)	58	–10*	–12 to –7
Systolic blood pressure	Saline (S)	100	–3	–6 to 1
(mm Hg)	Tramadol 100 mg (T1)	96	9*	5 to 12
	Tramadol 200 mg (T2)	103	11*	8 to 15
Median power (F50)	Saline (S)	0 81	–2	–14 to 12
(Hz)	Tramadol 100 mg (T1)	1 01	45*	27 to 66
	Tramadol 200 mg (T2)	0.92	69*	48 to 93
Spectral edge (F95)	Saline (S)	12 1	–1	–6 to 7
(Hz)	Tramadol 100 mg (T1)	10 1	17*	10 to 25
	Tramadol 200 mg (T2)	9.8	29*	21 to 37
Delta power (DP)	Saline (S)	61.1	6	0 to 13
(% total power)	Tramadol 100 mg (T1)	62.4	–3	–9 to 3
	Tramadol 200 mg (T2)	67 1	–13#	–18 to –7
Alpha:Delta ratio (A/D)	Saline (S)	0.37	–16	–30 to 2
	Tramadol 100 mg (T1)	0 38	21*	2 4 to 45
	Tramadol 200 mg (T2)	0 39	65*	39 to 97
Pa amplitude (Pa)	Saline (S)	0.24	–1	–10 to 10
(µv)	Tramadol 100 mg (T1)	0.2	4	–6 to 16
	Tramadol 200 mg (T2)	0 30	–3	–13 to 8
Pa latency (Pal)	Saline (S)	38 1	8	–3 to 20
(ms)	Tramadol 100 mg (T1)	35.1	5	–5 to 17
	Tramadol 200 mg (T2)	40 5	–7	–14 to 3
Nb amplitude (Nba)	Saline (S)	0 23	–1	–10 to 9
(µv)	Tramadol 100 mg (T1)	0.24	–1	–10 to 9
	Tramadol 200 mg (T2)	0.26	–2	–11 to 8
Nb latency (Nbl)	Saline (S)	54 7	6	–5 to 18
(ms)	Tramadol 100 mg (T1)	53 8	5	–6 to 17
	Tramadol 200 mg (T2)	59.4	–5	–15 to 6

Haemodynamic variables

Our data showed significant changes in systolic arterial pressure and heart rate after tramadol injection (BP: $P<0.001$; HR: $P<0.001$), and a significant linear trend between the saline, 100 mg and 200 mg groups (BP: $P<0.01$; HR: $P<0.05$).

EEG variables

There were no significant changes in the saline group. In contrast, both tramadol groups showed significant changes from pre- to post-injection in all variables ($P<0.001$ in all cases) bar delta power, in which the change was only significant with a 200 mg dose ($P<0.05$) (see Table 2). These changes were dose graduated in all cases, with a significant linear trend in each variable ($S \rightarrow T1 \rightarrow T2$; $P<0.001$).

AER variables

There were no significant differences in pre- to post-dose values for any of the AER variables (Table 2).

Discussion

Our results clearly show the alpha-adrenergic effects associated with tramadol administration at clinically used doses. They are similar to those of Coetzee *et al.*[2] in that tramadol produces evidence of activation in all the derived EEG variables. These changes are not clinically indicative of awakening or awareness.[7]

Interestingly, no significant changes in the AER variables measured were seen. Previous studies[8] in our unit have shown Pa amplitude increases of 53% with succinylcholine, 36% with laryngoscopy and 60% with intubation. This study would have been sensitive enough to detect an increase in Pa amplitude of 21% at the 5% significance level with a power of 80%. These patients were not undergoing surgery, nor were they intubated. These potent and variable stimuli tend to lighten anaesthesia[5] and this study excludes any AER changes due to these stimuli from the analysis.

Reviewing the papers mentioned in the introduction, we note that Coetzee and colleagues[2] thought that the EEG changes seen, although statistically significant, were not clinically significant. Lehmann's paper[3] states that 65% of patients had recall of music played to them, as opposed to none in the placebo group. It should be noted, however, that the only other analgesic/anaesthetic used in Lehmann's study was fentanyl and droperidol premedication, and ventilation with 79% nitrous oxide in oxygen. We do not feel this in any way represents standard or 'normal' anaesthetic practice for healthy patients undergoing elective orthopaedic or abdominal surgery. A more recent paper[9] shows no increased speed of awakening or orientation in patients given tramadol at the end of a procedure as opposed to those given morphine.

In conclusion, our work does not support lightening of anaesthesia due to tramadol and it agrees with the work of others using different techniques.

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Haemorrhage and risk factors associated with retrobulbar/peribulbar block: a prospective study in 1383 patients

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Patients undergoing intraocular surgery are elderly and may have disease or be receiving medication which increases the risk of haemorrhage. We interviewed 1383 consecutive patients scheduled for eye surgery requiring retrobulbar/peribulbar block about their use of non-steroidal anti-inflammatory drugs, oral steroids and warfarin. A history of diabetes mellitus and globe axial length was noted. Medial peribulbar and inferolateral retrobulbar blocks were performed by three specialists and six doctors in training. The ensuing haemorrhages were graded as follows: 1=spot ecchymosis; 2=lid ecchymosis involving half of the lid surface area or less; 3=lid ecchymosis all around the eye, no increase in intraocular pressure; 4=retrobulbar haemorrhage with increased intraocular pressure. Acetylsalicylic acid was taken by 482 (35%) patients, non-steroidal anti-inflammatory drugs by 260 (19%) and warfarin by 76 (5.5%). Lid haemorrhages (grades 1–3) were observed in 55 patients (4.0%); in 33 of these patients the haemorrhages were spotlike (grade 1). No grade 4 haemorrhages occurred. The preoperative use of acetylsalicylic acid, non-steroidal anti-inflammatory drugs or warfarin, whether or not they had been discontinued, did not predispose to haemorrhage associated with retrobulbar/peribulbar block.

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Patients scheduled for intraocular surgery are often elderly and may have concurrent diseases. In the Finnish population aged over 65 yr, non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed to 27.9% of people, mostly for degenerative musculoskeletal diseases (Prescription Register, 1996, Social Insurance Institution, Finland). In this age-group, warfarin is used for anticoagulation by 5.0% of people in order to prevent thromboembolism, and a low dose of acetylsalicylic acid is used by 4.9% to prevent myocardial infarction and cerebrovascular ischaemic events (Prescription Register, 1996, Social Insurance Institution, Finland). Haemorrhage is a rare complication of regional ophthalmic anaesthesia: lid ecchymoses (2.3–3.5%)[1] and retrobulbar haemorrhage (0.44–1.7%)[2 3 4] are the most common. As the benefits of retrobulbar/peribulbar block may outweigh the risk of puncture-induced haemorrhagic complications, even in patients on anticoagulant medication, we undertook a prospective study of the relationship between the use of anticoagulant drugs and bleeding associated with retrobulbar/peribulbar block. We assessed the influences of known risk factors related to the patients (e.g. anticoagulant medication, extended axial length of the eye) and the experience of the physician performing the block on the incidence of bleeding.

Patients and methods

Approval of the hospital ethics committee was obtained for the study. During 4 months of 1997 at Helsinki University Eye Hospital, 1383 consecutive patients scheduled for eye surgery or laser treatment under retrobulbar/peribulbar block were interviewed about their use of acetylsalicylic acid, NSAIDs, paracetamol, warfarin and oral steroids and their self-estimated tendency to develop haematomas. On the morning of operation, thromboplastin time (Stago Prothrombin Complex Assay, Diagnostica Stago, Asnieres, France) was measured from blood samples of the patients taking warfarin. In our hospital, patients are advised to discontinue warfarin for 2 days and acetylsalicylic acid for 3 days before surgery. Non-compliance with these rules does not usually lead to cancellation of surgery. Data on ophthalmic diagnosis and surgical procedure, existing diabetes mellitus, globe axis length, sex and age were recorded. It is considered difficult to perform retrobulbar

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injection if the globe axial length exceeds 26 mm,[5] and in such cases it is more likely that repeated attempts will be needed to perform the injection than in patients with normal anatomy.

The appearance and size of the haemorrhages were assessed on a four-grade scale: 1=spot ecchymosis; 2=lid ecchymosis involving half the lid surface area or less; 3=lid ecchymosis all round the eye, no increase in intraocular pressure; 4=retrobulbar haemorrhage with increased intraocular pressure. Nine doctors performed the blocks; three were experienced anaesthetists and six were doctors in training (four anaesthetists and two ophthalmologists).

Transconjunctival retrobulbar/peribulbar block was performed as described previously.[6] First, a medial peribulbar puncture was made with a sharp, disposable, 12-mm, 30-gauge needle (Microlance®; Becton Dickinson, Drogheda, Ireland) in the near perpendicular direction of the frontal plane, followed by inferolateral retrobulbar insertion of a sharp, disposable, 31-mm, 27-gauge needle (PrecisionGlide®; Becton Dickinson, Franklin Lakes, NJ, USA). The local anaesthetic used was a 1:1 mixture of 0.75% bupivacaine and 2% lidocaine with hyaluronidase 0–7.5 IU ml^{-1}. The maximum total volume of local anaesthetic was adjusted according to the lean body weight of the patient: 6 ml for patients under 70 kg body weight, 7 ml for patients between 70 and 80 kg, and 8 ml for those over 80 kg. As the local anaesthetic was injected, the anaesthetist palpated the lid with his finger, and if increased pressure was sensed the injection was stopped. Orbital compression of 25 mm Hg for 10 min was accomplished with an autopressor (Autopressor®; Storz, Heidelberg, Germany), except in patients who had had an operation on the same eye during the last 6 months. All patients were monitored using finger-pulse oximetry, continuous end-expiratory carbon dioxide using tubing in the nostril, electrocardiography, and non-invasive automatic blood pressure every 10 min. An intravenous cannula was inserted for the administration of sedatives or fentanyl as required. A stream of oxygen-enriched air (oxygen 2 litre min^{-1} + air 8 litre min^{-1}) was directed at the patient's face under the surgical drape.

The hypothesis was that use of anticoagulants and the preoperative discontinuation time do not affect the occurrence of haemorrhages (grades 1–4). Statistical analysis was undertaken with the Mann–Whitney rank sum, χ^2 and Fisher's exact tests, using SigmaStat for Windows, version 2.0 (Jandel Corporation). Values are expressed as mean (SD, range). A P value <0.05 was considered statistically significant.

Results

The physical characteristics and the ophthalmic diagnoses did not differ between patients with and without haemorrhage (Table 1). Senile nuclear cataract was the most common diagnosis (1061 patients (77%)), and most of the patients with this diagnosis (1029) underwent extracapsular operation by a phacoemulsification technique. The operation on one cataract patient was cancelled because of persisting nausea immediately after the block. One hundred and seventeen patients (7.8%) were excluded from the study. Seven patients gave insufficient history because of senile dementia, 27 had missing documentation about the haemorrhages, and 83 patients had other data missing.

Table 1 Physical characteristics (mean (SD, range)) and ophthalmic diagnoses in patients with and without haemorrhage

	Haemorrhage (n=55)	**Non-haemorrhage (n=1328)**
Age (yr)	71 (12, 37–93)	71 (13, 15–95)
Male/female (per 100)	36/64	33/67
Globe axial length (mm)	23 (1.1, 21–26)	23 (1.7, 19–34)
Cataract and other anterior segment disorders (n)	44 (4.0%)	1061 (96.0%)
Posterior segment disorders (n)	7 (4.7%)	142 (95.3%)
Glaucoma (n)	3 (2.9%)	102 (97.1%)
Strabismus (n)	1 (4.2%)	23 (95.8%)
Total (n)	55 (4.0%)	1328 (96.0%)

The overall frequency of haemorrhages was 4.0% (55 of 1383 patients). The haemorrhages were distributed into the following grades: grade 1, 33 patients; grade 2, 15 patients; grade 3, 7 patients. No high-pressure retrobulbar haemorrhages (grade 4) occurred in this series. Only one scheduled operation was cancelled because of haemorrhage (grade 3), although the intraocular pressure was only 13 mm Hg and no decompressive operative measures were needed. It was noted that this patient sneezed during the peribulbar injection. In the preoperative interview, a haemorrhagic tendency was reported by 32% of patients but it did not predispose to haemorrhage. Trainees did not evoke significantly more haemorrhages (4.7%) than staff anaesthetists (3.8%).

Use of more than one drug that may affect coagulation was characteristic of this patient population (Table 2). Also, the drug-free preoperative period varied considerably. The drug category, the time of discontinuing drug therapy and the use of various combinations of drugs did not affect significantly the occurrence of haemorrhage. Warfarin was used by 5.5% of the patients and its use did not predispose to haemorrhage (Table 2). The mean thromboplastin time value in patients who had haemorrhage (35% (19, 20–56)) did not differ significantly from that of patients who had no haemorrhage: (39% (16, 14–81)). The prevalence of diabetes mellitus was 22% in patients receiving warfarin, and cortisone was used continuously by 3.9% of diabetics receiving warfarin. Among the latter subgroup (three patients), none developed any detectable haemorrhage from the block. Table 2 shows the frequencies of concomitant use of warfarin with acetylsalicylic acid, NSAIDs or paracetamol.

Oral steroids were used by 4.2% of the patients but did not predispose to haemorrhage (1.7%). Patients on cortisone therapy, however, reported a haemorrhagic

Table 2 Preoperative anticoagulants and haemorrhage

Treatment	No. of patients (%)	Haemorrhages (%)
Total no of patients	1383 (100%)	55 (4.0%)
Receiving warfarin	76 (5.5%)	3 (3.9%)
Not stopped	5 (6.6%)	0
Stopped 1 day	7 (9.2%)	1 (14.3%)
Stopped 2 days	14 (18.4%)	1 (7.1%)
Stopped 3 days	21 (27.6%)	0
Stopped 4 days	4 (5.3%)	0
Stopped 6 days	1 (1.3%)	0
Stopped 7 days	1 (1.3%)	0
Missing discontinuation time	23 (30.3%)	1 (4.3%)
Receiving acetylsalicylic acid	482 (34.9%)	18 (3.7%)
Stopped 0–2 days	139 (28.8%)	7 (5.0%)
Stopped 3–14 days	343 (71.2%)	11 (3.2%)
Receiving NSAID	260 (18.8%)	11 (4.2%)
Stopped 0–2 days	191 (73.5%)	9 (4.7%)
Stopped 3–14 days	69 (26.5%)	2 (2.9%)
Receiving paracetamol	101 (7.3%)	5 (5.0%)
Stopped 0–2 days	80 (79.2%)	5 (6.3%)
Stopped 3–14 days	21 (20.8%)	0
Receiving warfarin alone	47 (3.4%)	0
Receiving acetylsalicylic acid alone	367 (26.5%)	15 (4.1%)
Receiving NSAID alone	157 (11.4%)	6 (3.8%)
Receiving paracetamol alone	59 (4.3%)	2 (3.4%)
Receiving warfarin + acetylsalicylic acid	4 (0.3%)	0
Receiving warfarin + NSAID	9 (0.7%)	1 (11.1%)
Receiving warfarin + paracetamol	16 (1.2%)	2 (12.5%)
Receiving no warfarin but receiving		
acetylsalicylic acid + NSAID + paracetamol	1 (0.1%)	0
acetylsalicylic acid + NSAID	89 (6.4%)	3 (3.4%)
acetylsalicylic acid + paracetamol	21 (1.5%)	0
NSAID + paracetamol	4 (0.3%)	1 (25.0%)
Not using any of these medicines	609 (44.0%)	25 (4.1%)

tendency significantly more often than those receiving no steroids (56 and 32% respectively ($P<0.001$)). Cortisone use was significantly more frequent among diabetics than non-diabetics (7.5 and 3.6% respectively ($P=0.021$)). The prevalence of diabetes mellitus in the whole sample was 15%, and the incidence of haemorrhage in the diabetic group was 4.5%.

Discussion

The overall incidence of lid haemorrhages in our study (4.0%) was similar to the incidences in earlier reports (2.3–3.5%).[1] Preoperative use of acetylsalicylic acid or other NSAIDs did not increase the frequency and grade of haemorrhages associated with retrobulbar/peribulbar block. The interval from discontinuation of these drugs until surgery did not affect haemorrhage.

It can be assumed that visible haemorrhages do not always appear within 10 min (duration of autopressor compression) after injecting the block and a few cases may have remained undetected, especially those presenting as minor spot-like haemorrhages. The physician performing the retrobulbar/peribulbar block graded the occurrence and size of the haemorrhage. We are aware that a non-blinded assessment could have been biased and, to some extent, led to underestimation of iatrogenic complications. But the observed frequency of haemorrhages, as evaluated 10 min after the injection, is probably accurate. It is also possible that patients who had taken acetylsalicylic acid and/or NSAIDs 1–2 weeks before surgery were registered as non-users. Elderly patients may not remember occasional use of these drugs. Such assumed inaccuracy of the data may make the results somewhat less powerful. Haemorrhages were as frequent in patients taking warfarin as in those who were not. More than 500 patients receiving warfarin should have been included in this study in order to make any conclusion about the necessity of stopping warfarin preoperatively. Furthermore, if more patients had been included it may have been possible to detect any interaction of warfarin and platelet aggregation inhibitors in provoking haemorrhage.

A large retrobulbar haemorrhage may delay a planned eye operation,[2] and may cause compression of the circulation[7] or optic atrophy[8] leading to permanent blindness. The prevalence of retrobulbar haemorrhage after retrobulbar injection has been reported to vary from 0.44 to 1.7%.[2–4] In a retrospective study 60 retrobulbar haemorrhages were induced by a retrobulbar block (1.7% of all retrobulbar blocks). Warfarin, acetylsalicylic acid and NSAIDs were stopped 14 days before surgery. The study included a control group of 60 patients. Thirty per cent of patients with haemorrhage received at least one of these drugs, whereas these drugs were taken by only 20% of the patients in the control group.[4]

Platelet cyclo-oxygenase is acetylated irreversibly by acetylsalicylic acid. Cyclo-oxygenase inhibition by NSAIDs leads to reversible disturbance of platelet aggregation.[9] A healthy individual produces platelets at the rate of about 70×10^9 litre^{-1} per day and a concentration of normal functioning platelets of $30–50\times10^9$ litre^{-1} is adequate for normal clotting.[10] Forty-eight hours should, therefore, be sufficient for the recovery of clinically adequate thrombocyte function after the last mini-dose of acetylsalicylic acid.[10] There have been no large-scale studies of the influence of the duration of discontinuation of acetylsalicylic acid, other NSAIDs and warfarin on haemorrhage during retrobulbar/peribulbar blocks. But there are some similarities between retrobulbar/peribulbar and epidural blocks. Whereas the use of warfarin at therapeutic doses contraindicates epidural block, the use of acetylsalicylic acid and other NSAIDs up to the day of the block may be considered safe in patients undergoing epidural block.[11 12] Acetylsalicylic acid 60 mg day^{-1} is not associated with a significant increase in bleeding during epidural anaesthesia.[11] The use of antiplatelet therapy in patients undergoing spinal or epidural anaesthesia has not been found to be associated with an increased incidence of spinal haematoma.[12] However, acetylsalicylic acid medication has been reported to increase bleeding at the operation site.[13–15] In contrast, there is some disagreement about the role of other NSAIDs in surgical bleeding, but on the whole it does not increase it.[16–19] The exception is a report of 41 hysterectomy patients who received indomethacin preoperatively for postoperative analgesia.[20]

As a result of complications associated with retrobulbar block, several alternative techniques have been developed, such as the use of a curved needle. This was associated with a very low frequency of haemorrhages (lid ecchymosis 2%).[21] Topical anaesthesia is also free from anaesthesia-related haemorrhage. However, the sub-Tenon method of regional ophthalmic anaesthesia may not be an option for reducing the risk of haemorrhage when compared with retrobulbar/peribulbar anaesthesia.[22]

In our practice there seems to be no reason to limit the use of acetylsalicylic acid or other NSAIDs before retrobulbar/peribulbar block. On the other hand, our study supports the assumption that preoperative discontinuation of warfarin for 2 days preoperatively might be sufficient to maintain haemostasis to prevent bleeding during retrobulbar/peribulbar block.

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Xenon does not induce contracture in human malignant hyperthermia muscle[†]

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Xenon has many characteristics of an ideal anaesthetic agent. It is not known whether xenon is a safe alternative to the potent inhalational anaesthetics in patients susceptible to malignant hyperthermia (MH). We investigated the effect of xenon, halothane and caffeine on muscle specimens of 31 individuals, referred to the MH Unit of the University of Ulm, and performed genetic epidemiology. Thirteen individuals were classified as MH susceptible and 18 as MH negative. Xenon 70% did not cause an increase in baseline tension of any MH-susceptible muscle specimen in contrast to halothane and caffeine. The evoked twitch response increased transiently in MH-susceptible and normal specimens indicating a mechanism independent of MH susceptibility. These results suggest that xenon, in concentrations up to 70% may be a safe anaesthetic for MH-susceptible patients.

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Malignant hyperthermia (MH) is an autosomal dominant, pharmacogenetic disorder of skeletal muscle. First recognized in 1960,[1] MH is triggered by volatile anaesthetics and depolarizing muscle relaxants leading to a life-threatening hypermetabolic state[2] with a clinical age-dependent incidence of ranging from 1 in 3000 to 1 in 100 000 anaesthetics.[3–5]

The main causative gene (RYR1) encodes the high molecular weight ligand-gated calcium channel, the ryanodine receptor type 1[6 7] located in the sarcoplasmic reticulum (SR). Over 20 mutations have been reported in the RYR1 gene on chromosome 19q12-13.2, accounting for approximately 20% of all cases. By linkage, more than 50% of families are linked to RYR1[8 9] indicating that many mutations are unidentified. Two mutations in the gene on chromosome 1q encoding the α_1-subunit of the skeletal muscle dihydropyridine receptor (DHPR) have also been described, each in a single pedigree (for review see[10]). In the muscle, volatile anaesthetics cause an increase in myoplasmic calcium concentration[11] leading to muscle contracture and hypermetabolism. These effects are utilized in the in-vitro contracture test (IVCT)[12], the diagnostic gold standard.[13]

Since 1939 the inert gases have been known to exert anaesthetic properties at hyperbaric pressure.[14] In addition, xenon produces anaesthesia at atmospheric pressure.[15] Xenon was first used for anaesthesia in man in 1951.[16] It causes no significant increases in plasma catecholamine concentrations or adverse effects on myocardial function.[17] With a minimum alveolar concentration (MAC) of 71%, it is more potent than nitrous oxide (MAC 105%) and its very low blood/gas solubility coefficient (0.14 *vs* 0.47 of N_2O) leads to rapid induction and recovery from anaesthesia. However, its high cost has prevented its use in routine clinical practice. The development of recycling devices, closed circuit anaesthesia systems, new preparations, such as lipid-bound i.v. solutions, and the decrease in cost of xenon indicate that this may change.[18] One possible use is as an alternative to potent inhalational anaesthetics in MH-susceptible patients. To test the potential of xenon to trigger MH, we investigated the effect of xenon on muscle specimens of MH-susceptible patients and normal individuals in the IVCT.

Methods

With approval by the Ethics Committee of the University of Ulm, 31 patients referred to the MH Unit of the University of Ulm for assessment of MH susceptibility, consented to

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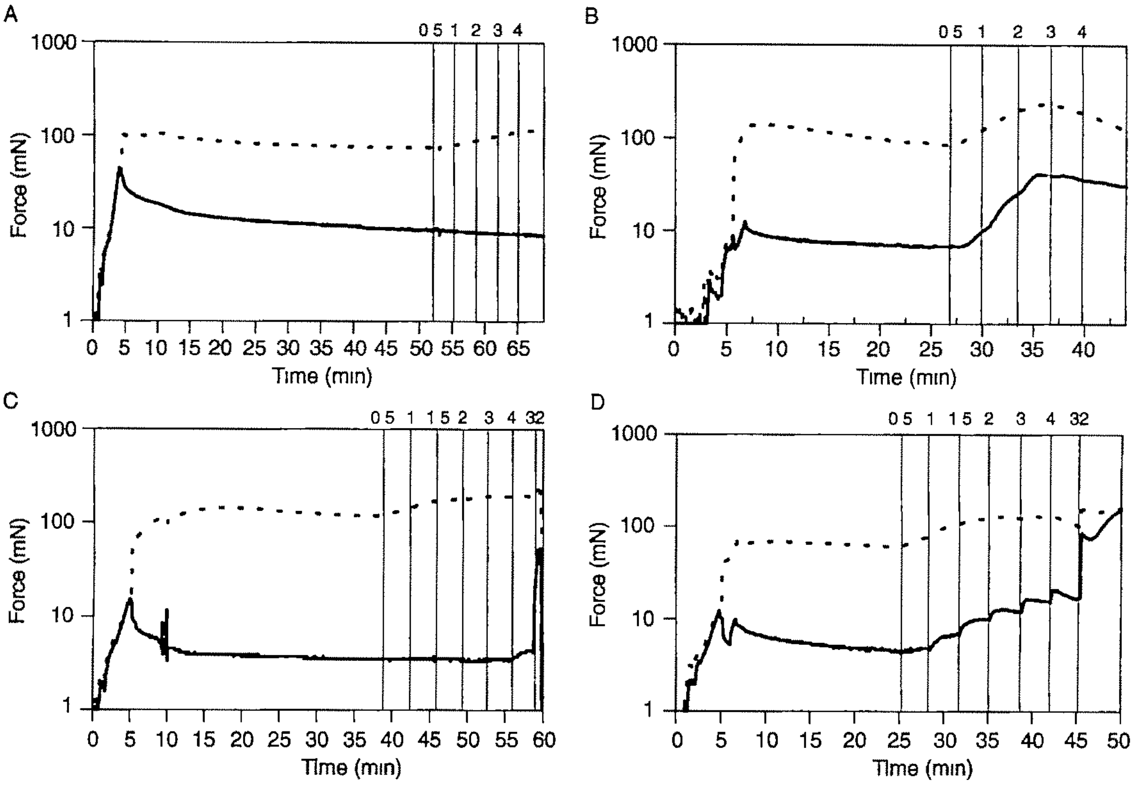

Fig 1 IVCT trace of a MHN (A) and MHS (B) muscle specimen during exposure to halothane (0.5–4.0%) MHS specimens showed a marked increase in baseline tension and twitch force The vertical lines indicate the application of the halothane concentration specified on top of the graph (in %). IVCT trace of a MHN (C) and MHS (D) muscle specimen during exposure to caffeine (0.5–32 mM) MHS specimens showed a marked increase in baseline tension and twitch force The vertical lines indicate the application of the caffeine concentration specified on top of the graph (in mM).

participate in this study. The patients belonged to 28 non-related families. No patient had a clinically evident, neuromuscular disease.

In vitro contracture test

Muscle bundles were excised from the quadriceps muscle under regional anaesthesia (3 in 1-block: 1% prilocaine plus 0.5% bupivacaine). The IVCT was performed on viable muscle fascicles (twitch response to supramaximal electrical stimulation ≥10 mN) according to the European MH Group protocol.[12] Muscle strips were stretched to 150% of their initial length and electrically stimulated (frequency 0.2 Hz, square pulse, 1 ms duration). After equilibration, administration of halothane (cumulative: 0.5, 1, 2, 3, and 4% v/v equivalent to muscle bath concentrations of 0.11, 0.22, 0.44, 0.66 and 0.88 mM) or caffeine (cumulative: 0.5, 1.0, 1.5, 2.0, 3.0, 4.0 and 32 mM) was started and the baseline tension prior to drug application and at each drug concentration was measured continuously using a force transducer (Fa. RS Biomed Tech, Sinzing, Germany). The halothane concentration was increased at 3-min intervals and monitored by infrared spectroscopy (Iris, Draeger, Luebeck, Germany). Additionally, the concentrations of halothane in the muscle bath were checked by gas chromatography. Caffeine was added cumulatively for each concentration (3 min) from a freshly prepared and warmed stock solution (100 mM at 37°C). The concentration of caffeine in the bath solution was determined by UV-spectrophotometry. MH status was assigned according to the European MH group protocol: MH*S* (MH susceptible) muscle showed abnormal contractures of ≥2 mN in at least one muscle specimen exposed to halothane ≤2 mM *and* one exposed to caffeine ≤2 mM, MH*E* (MH equivocal) only to halothane (MHE*h*) *or* caffeine (MHE*c*) and MH*N* (normal) muscle strips showed no abnormal response.

Xenon test

A xenon test was performed with one or two viable and supernumerary muscle strips of each individual tested by the standard IVCT. Xenon was obtained from Messer-Griesheim (Duisburg, Germany) in a composition of 70% xenon, 25% oxygen and 5% carbon dioxide which, by its buffering capacities, plays an important role in stabilizing the pH of the bath solution. The preparation, stretching and stimulation of the muscle bundles were done as described for the dignostic IVCT. After equilibration of the muscle bundle (a baseline tension decrease of <2 mN over 10 min) the gassing mixture was switched from carboxygen (95% oxygen, 5% carbon dioxide) to the xenon mixture for 10 min. Baseline tension and evoked twitch force were recorded continuously.

Genetic testing

All families were tested for the following mutations on the RYR1 gene by restriction enzyme analysis or single strand conformation analysis (SSCA) on genomic DNA according to the methods of Brandt and co-workers:[19] Cys35Arg, Arg163Cys, Gly248Arg, Gly341Arg, Ile403Met, Tyr522-Ser, Arg533His, Arg552Trp, Arg614Cys, Arg614Leu, Arg2163Cys, Arg2163His, Arg2163Pro, Val2168Met, Thr2206Met, Thr2206Arg, Gly2434Arg, Arg2435His, Arg2435Leu, Arg2454His, Arg2454Cys, Arg2458Cys and Arg2458His. Additionally, all families were screened for the presence of the Arg1068His and Arg1086Cys mutations in the gene encoding the α_1-subunit of the L-type voltage-dependent calcium channel (dihydropyridine receptor, DHPR). Each patient from a family with a known mutation was individually tested for the presence of this mutation. Genomic DNA was isolated from blood preserved in ethylenediamintetraacetic acid.

Statistics

The increase in evoked twitch force is presented as the percentage change in comparison to the force before application of the test agents (predrug *vs* postdrug value). A contracture was determined as the change in baseline tension from the lowest value reached during the test. Intergroup comparisons were performed with the Student's *t*-test for unpaired samples. A *P* value <0.05 was considered to indicate statistical significance. All analyses were performed with StatView 4.5™ (Abacus Concepts, Berkeley, CA, USA).

Results

IVCT

Typical IVCT traces for halothane and caffeine are plotted in Figure 1. During exposure to either substance, the MHS strips initially show a more pronounced evoked twitch force increase compared to MHN, but reach a plateau and then decrease due to the development of contractures. The evoked twitch force in MHN specimens, in the absence of contractures, increases with increasing drug concentration (Figure 2). The medians and interquartile ranges of the contractures in the 13 MHS and 18 MHN individuals are presented in Table 1.

Xenon test

Following application of 70% xenon, no increase in baseline tension, i.e. contracture, was observed in muscle specimens of MHS patients or MHN individuals (Table 1). The evoked twitch force, however, showed a slight, but transient increase compared to the predrug force which was more pronounced in muscle specimens of MHS patients than of MHN individuals: the median of the maximal increase was 56.7% and 33.5%, respectively (Table 1). To demonstrate the viability of MHS specimens used in the xenon tests, 3% halothane was administered after discontinuation of xenon and was found to cause a contracture in all cases (Fig. 3c).

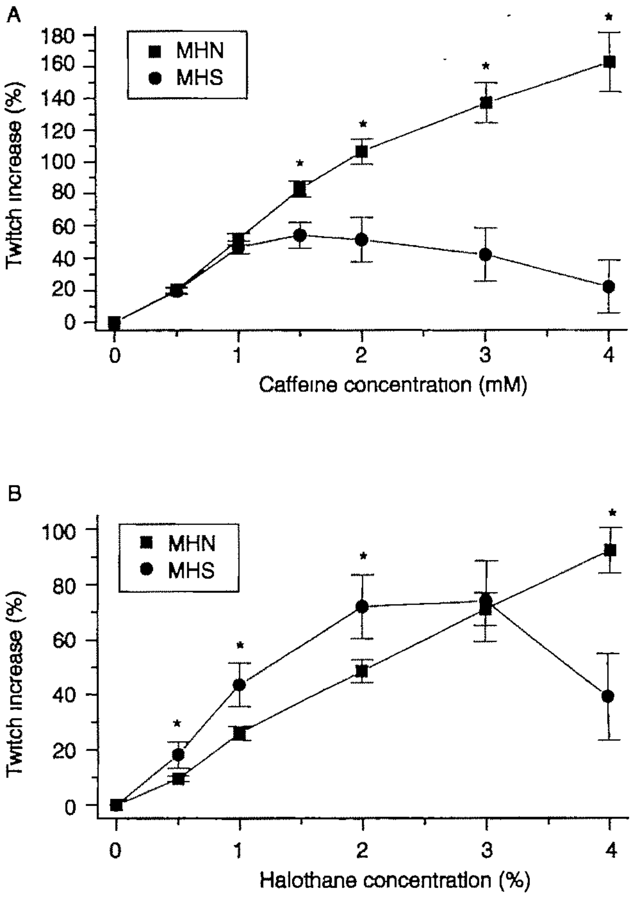

Fig 2 Dose-response curves of the twitch force due to exposure to caffeine (A) and halothane (B) Twitch force increase is given in percent relative to the predrug value. Error bars indicate SEM. Values that are significantly different are marked by an asterisk (*).

Genetic testing

Screening of the 28 families for all known RYR1 and two DHPR mutations (α_1-subunit) revealed the Gly2434Arg mutation in three MHS patients, belonging to two unrelated families, and the Arg614Cys mutation in two unrelated patients. All of these patients had a positive IVCT result (MHS). No other mutation could be detected.

Discussion

Contractures in the IVCT are induced by increases of myoplasmic calcium and therefore represent a simple *in vitro* model for testing the potential of anaesthetic agents to trigger an MH episode. Therefore, if xenon also causes a pathological increase in myoplasmic calcium, contractures in the IVCT should be expected. However, in our investigations, we found no contractures in either muscle strips of

Table 1 Baseline contracture and twitch force increase of the muscle bundles after exposure to halothane, caffeine or xenon. Values are given as median 25th and 75th centiles are noted in brackets. *P*-values of the unpaired *t*-test MHS *vs* MHN are indicated

MH status	Contracture (mN)			Twitch force increase (%)		
	Halothane (2%)	Caffeine (2 mM)	Xenon (70%)	Halothane (2%)	Caffeine (2 mM)	Xenon (70%)
MHN	–0 8	–1 0	–0.6	43 6	104.5	33 5
(*n*=18)	(–1 1 / 0)	(–2 0 / 0.4)	(–0.9 / –0.1)	(35.9 / 65.4)	(80.1 / 125 2)	(24 5 / 45 6)
MHS	6.3	6.2	–0.9	63.6	60 1	56 7
(*n*=13)	(3.7 / 15 3)	(2.5 / 11 7)	(-1 5 / –0.2)	(46 6 / 98.2)	(30 15 / 71.3)	(41.0 / 62.4)
P-value	0.003	0.007	0 25	0 026	0.005	0.015

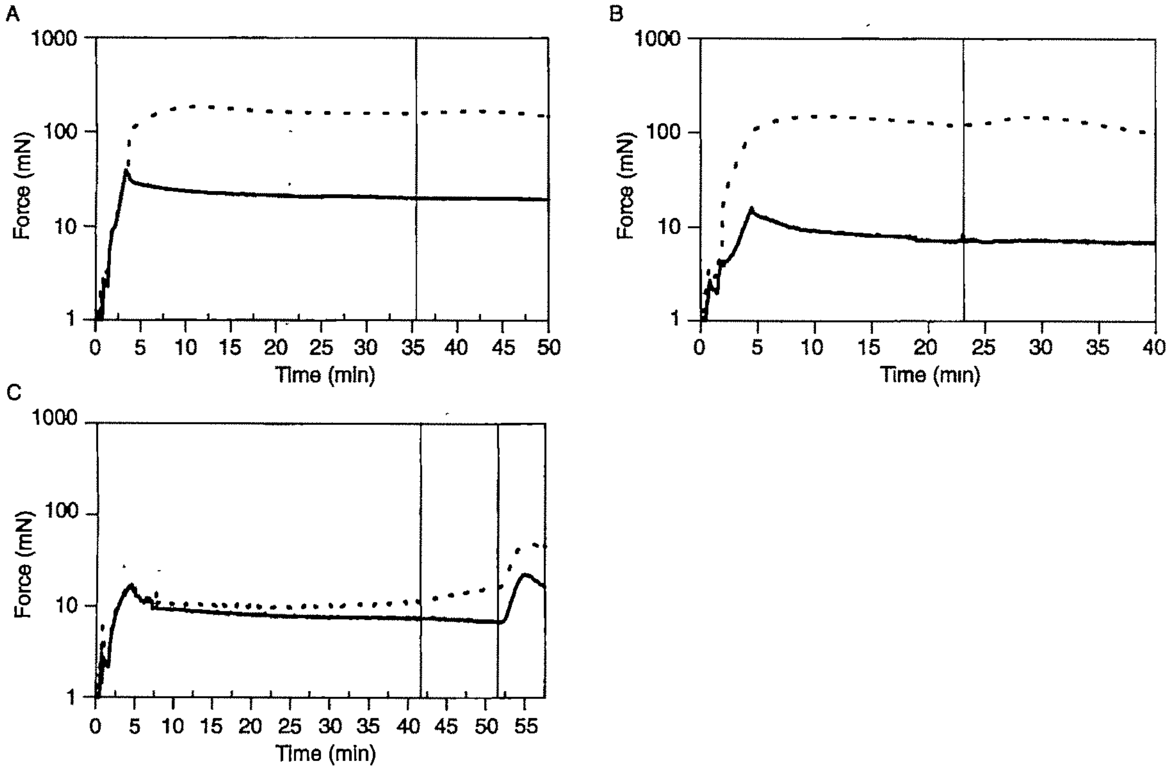

Fig 3 IVCT trace of a MHN (A) and MHS (B) muscle specimen during exposure to xenon (70%). No increase in baseline tension, but a slight increase in twitch force is notable. The vertical line indicates the start of the application of 70% xenon. IVCT trace of a MHS (C) muscle specimen during successive exposure to xenon (70%) and subsequently to halothane (3%). A marked increase in baseline tension is visible only after halothane exposure The first vertical line indicates the start of the application of 70% xenon, the second indicates discontinuation of xenon and simultaneous start of 3% halothane exposure.

MH susceptible patients or in normal individuals despite proof of contracture responsiveness of the tested MHS bundles.

Four of the 11 tested MHS families (36%) carried one of the two most common RYR1 mutations (Arg614Cys or Gly2434Arg). This frequency of mutations in the investigated patients corresponds to those previously reported.[19] The samples tested may therefore be considered representative of the MH population.

The application of all three test agents increased the evoked twitch force in the IVCT, a phenomenon presumably due to slight, but controllable elevation of sarcoplasmic calcium release.[20] Remarkably, this effect is consistently more pronounced in MHS specimens than in MHN, but the increase induced by xenon in its maximal clinically applied dose is significantly smaller than that observed with either halothane or caffeine. The evoked twitch force increase on application of xenon indicates the substance readily penetrates the muscle strip and lack of penetration is unlikely to be the reason for lack of contracture in response to xenon. Recently, xenon was shown to inhibit plasma membrane calcium-ATPase (PMCA) leading to increased resting $[Ca^{2+}]_i$, enhanced peak $[Ca^{2+}]_i$, and delayed reuptake following stimulation in brain tissue.[21] As an increase in intracellular calcium in skeletal muscle could lead to an increase in muscle force and as PMCA is also present in skeletal muscle, this mechanism, independent of RYR1, could be responsible for the observed evoked twitch force increase in accordance with earlier findings of passive non-ryanodine receptor-mediated calcium release in MH.[22]

In vivo effects of xenon on MH susceptible patients have not yet been tested. In an animal model of MH, the purebred Landrace, Pietrain and Poland China pigs,[23] Froeba and co-workers[24] have demonstrated the complete absence of any haemodynamic, gas-exchange or metabolic response indicative of MH during 2 h of xenon administration. In contrast, in all animals the subsequent administration of halothane initiated fatal MH episodes. Considering the results of the *in vivo* experiments in the pig model and the *in vitro* results in humans, it is reasonable to conclude that xenon (up to 70%) will not trigger MH during anaesthesia in man.

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Urinary, biliary and faecal excretion of rocuronium in humans

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The excretion of rocuronium and its potential metabolites was studied in 38 anaesthetized patients, ASA I–III and 21–69 yr old. Rocuronium bromide was administered as an i.v. bolus dose of 0.3 or 0.9 mg kg^{-1}. In Part A of the study, the excretion into urine and bile, and the liver content were studied. Plasma kinetics (n=19) were similar to those reported previously. Urinary recovery within 48 h after administration was 26 (8)% (mean (SD)) (n=8) of the dose. In bile obtained from T-drains, the recovery within 48 h was 7 (6)% (n=11). The rocuronium concentration in bile declined bi-exponentially, with half-lives of 2.3 (0.7) and 16 (11) h respectively (n=6). In three patients from whom stoma fluid was collected, the amount of rocuronium recovered ranged from 0.04 to 12.0% of the dose. In liver tissue obtained from four patients undergoing hemihepatectomy, the estimated amount of rocuronium at 2–5 h after administration ranged between 6.3 and 13.2% (n=4). In the second part of the study (Part B), urine and faeces were collected over 4–8 days and the recovery was 27 (13)% and 31 (23)% of the dose respectively (n=10). In most samples, irrespective of the type of biological material, only small amounts of the metabolite 17-desacetyl-rocuronium was found. The results demonstrate that rocuronium is taken up by the liver and excreted into bile in high concentrations. The faecal and urinary excretion of unchanged rocuronium are the major routes of rocuronium elimination.

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Keywords: neuromuscular block, rocuronium; pharmacokinetics, rocuronium; metabolism, rocuronium

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Rocuronium, the 2-morpholino, 3-desacetyl, 16-*N*-allyl-pyrrolidino derivative of vecuronium, is a non-depolarizing neuromuscular blocking agent with a rapid onset of action, and a duration similar to that of vecuronium. The pharmacokinetics of rocuronium have been studied extensively during the last decade, both in animals[1 2 33] and in man.[3–18] Until the present time, knowledge of the routes of elimination of rocuronium has been limited to animal data and to urinary excretion data in man.

In animals, 9–25% of radiolabelled rocuronium was found in urine, and 65–75% in faeces (unpublished observations, Organon Teknika). Rocuronium was rapidly taken up by isolated perfused rat liver with a high extraction ratio and was also rapidly excreted into the bile.[2] In addition, *in vitro* experiments with human liver tissue have shown that rocuronium and vecuronium are rapidly taken up by hepatocytes by a carrier mediated process.[19 20] In man, the mean amounts excreted into urine were 12–22% of an 0.6 mg kg^{-1} dose and 31% of a 1 mg kg^{-1} dose of rocuronium within the first 12 h after administration, the major part being excreted within the first 2 h.[3 7 8]

On the basis of its chemical structure, rocuronium is expected to be metabolized into its 17-desacetyl derivative and possibly into its *N*-desallyl derivative. In man the rat and the dog, 17-desacetyl-rocuronium has been found in negligible amounts. To date, *N*-desallyl-rocuronium has not been detected in any experimental or clinical *in vivo* studies.

In clinical studies with vecuronium, bile samples were collected from patients where a T-drain was placed in the common bile duct in the course of surgery[21] However, during the last decade the surgical techniques for cholecystectomy and choledocholithiasis have changed significantly and choledochostomy with placement of a T-drain is seldom performed. In addition to bile sampling from a T-drain, it

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was therefore, necessary to employ other techniques to study the hepatic elimination of rocuronium and its potential metabolites such as: (i) direct sampling of bile by puncturing the common bile duct during laparoscopic surgery; (ii) collection of stoma fluid during and after surgery; (iii) taking liver tissue biopsies from patients undergoing partial hepatectomy; and (iv) collection and analysis of faeces over a postoperative period of 7 days.

On the basis of the above considerations the present study was designed in order to ascertain the fate of rocuronium in man with particular emphasis on the hepatic uptake and biliary excretion of the parent compound and its potential metabolites.

Patients and methods

The study was divided into two parts with different aims (Table 1).

Patients

Each study protocol had been approved by the Ethical Committee of the centre participating in the corresponding part of the study. In total, 38 patients (14 male, 24 female), ASA I–III and aged 21–69 (median 45) yr, weighing 51–105 (median 71) kg participated in the study after written informed consent had been obtained. Patients in Part A were scheduled for upper abdominal (including laparoscopic) or low ileostomy surgery under general anaesthesia, with either insertion of a T-drain in the common bile duct or formation of a small bowel stoma located at least 60 cm proximal to the ileocaecal valve, or patients where such a stoma was already present. Patients in Part B were scheduled for peripheral surgery and expected to remain in hospital for 7 days. Patients who were pregnant or breast-feeding, patients with a history of cardiovascular, renal, hepatic, metabolic or neuromuscular disorders, patients with a body weight more than 20% below or 35% over their ideal body weight (height in cm minus 100 equals weight in kg) and those receiving any medication interfering with neuromuscular function or with the HPLC analysis were excluded.

Anaesthesia

Following pre-oxygenation for 2 min, patients underwent either a rapid sequence induction or a routine induction of anaesthesia with sodium thiopental 3–5 mg kg^{-1} and fentanyl 2–3 μg kg^{-1} i.v. Intubation was facilitated with succinylcholine 1 mg kg^{-1}, pancuronium 80–100 μg kg^{-1} or rocuronium 0.9 mg kg^{-1}. Following intubation the patients were ventilated mechanically with 66% nitrous oxide in oxygen, supplemented with isoflurane (inspired concentration 0.5–0.8 vol% in Part A; 0.4–1.7 vol% in Part B). Adequate anaesthesia was maintained by fentanyl supplements as required. Ventilation was adjusted to maintain a normal end-tidal carbon dioxide and anaesthesia was adjusted to the requirements of the patient. In patients who had not received rocuronium on induction, rocuronium 0.3 mg kg^{-1} was administered after obtaining control (blank) samples of various body fluids. In all patients, rocuronium bromide (0.3 or 0.9 mg kg^{-1}) was administered over 10 s as a single bolus in a rapidly running i.v. infusion. Pancuronium or succinylcholine were administered for further muscle relaxation if required. ECG, blood pressure, heart rate, body temperature, fluid balance, electrolyte balance, and acid–base balance were monitored as part of the routine clinical management and were not evaluated further in this study.

Sampling

The type of samples taken depended on the type of surgery performed. A blank sample of all types of fluids was taken prior to rocuronium adminstration. Bile was collected from a T-drain which was inserted either during surgery or had been in place previously. Samples were taken at intervals for 48 h after the administration of rocuronium, thoroughly mixed, and the volume of bile was measured. Bile samples (2–3 ml) were also taken from the common bile duct during laparoscopic surgery while this duct was accessible to the surgeon. If possible, three samples at least 5 min apart, were collected. Stoma fluid was collected at intervals for 48 h after the administration of rocuronium. Samples were mixed thoroughly and the volume measured. In cases of partial liver resection, the surgeon was asked to provide a section of normal liver tissue. The liver tissue samples were carefully blotted dry and weighed. They were cut into small pieces and homogenized for 10 min with 1 M NaH_2PO_4 (1:9). The surgeon was asked to estimate the liver weight. Urine was collected at intervals for 48 h (Part A) or for 7 days (Part B) after the administration of rocuronium, mixed thoroughly, and the volume measured (each protocol). Blood samples (4 ml) were taken from a dedicated i.v. cannula at 1, 3, 5, 10, 15, 20, 30, 60, 120, 180, 240, 360 and 480 min after rocuronium administration (Part A). Faeces were collected for 7 days. After weighing and homogenization, samples were mixed with 1 M NaH_2PO_4 (Part B). All samples were acidified to prevent spontaneous hydrolysis of rocuronium with 0.2 ml of 1 M NaH_2PO_4 for every millilitre of sample taken, unless stated otherwise. Samples were frozen and stored at −18°C until analysis.

Rocuronium assay

Concentrations of rocuronium and its potential metabolites 17-desacetyl-rocuronium and *N*-desallyl-rocuronium in plasma, urine, bile, faeces, stoma fluid and liver homogenate were analysed by HPLC as described previously.[22] The assay accuracy, expressed as the percentage of the added amount recovered, varied from −14 to +14% (depending on concentration, matrix and compound) over the range of 25–1000 ng. The mean precision, as indicated by the within-

Table 1 Study design

	Part A	Part B
Special aims	Liver and bile collection	Prolonged (7 day) faeces and urine collection
Study centres	Belfast (n=7), Groningen (n=11), Linkoping (n=10)	Stockholm (n=10)
Surgery	Upper abdominal, ileostomy, biliary, hepatectomy	Peripheral
Rocuronium dose	0.3 mg kg^{-1} (n=11) 0.9 mg kg^{-1} (n=17)	0.9 mg kg^{-1}
Plasma kinetics	Yes (n=19)	No

Table 2 Total recovery of rocuronium and 17-desacetyl-rocuronium as percentage of the administered dose in urine and bile (Part A) and in urine and faeces (Part B). Mean values (SD) [range] (number of patients). [a]Ranging from 4–8 days after administration [b]Patients with evaluable recovery of both urine and bile (Part A) or urine and faeces (Part B)

	Part A		Part B
	Within 24 h	Within 48 h	Within 7 days[a]
Part A			
Urine	22 (7) [9–36] (n=14)	26 (8) [12–37] (n=8)	27 (13) [14–60] (n=10)
Bile	6 (6) [0.2–21] (n=11)	7 (6) [0.5–22] (n=11)	
Faeces			31 (23) [2–67] (n=10)
Total [b]	32 (5) [23–36] (n=7)	34 (6) [25–42] (n=6)	58 (28) [16–101] (n=10)

day coefficients of variation, was 6.8, 6.8 and 5.9% for rocuronium, 17-desacetyl-rocuronium and *N*-desallyl-rocuronium respectively. The lower limit of quantification (LOQ) for rocuronium, 17-desacetyl-rocuronium and *N*-desallyl-rocuronium were 10, 20, and 20 ng ml^{-1} in plasma, 25, 25, and 50 ng ml^{-1} in urine, 10, 25, and 25 ng ml^{-1} in bile, 50 and 50 ng ml^{-1} in faeces, 20 and 20 ng ml^{-1} in stoma fluid and 250 ng ml^{-1} in liver homogenate for all three compounds. (*N*-desallyl-rocuronium could not be quantified in faeces and stoma fluid due to interference by endogenous substances with similar retention times.)

Pharmacokinetic analysis

Plasma concentration–time data were analysed by Iterative Two-Stage Bayesian analysis using the program MultiFit (written by J. H. Proost). The mean values and variance-covariance matrix of the pharmacokinetic population parameters of a two-compartment model (CL, V_1, CL_{12}, V_2) and of a three-compartment model (CL, V_1, CL_{12}, V_2, CL_{13}, V_3)[23] and the residual variance were estimated by an iterative Bayesian procedure as described in the literature[24 25] using the plasma concentration–time data of each patient participating in this part of the study. A log-normal distribution for both the pharmacokinetic population parameters and the plasma concentration measurement errors was assumed. The correctness of the latter assumption was tested by visual inspection of the graphs of the residuals plotted against time and against concentration. Moreover, the relative error of the bioanalysis is known to be almost independent of concentration over the entire concentration range.[22] Goodness-of-fit was evaluated from visual inspection of the measured and calculated data points and of the residuals plotted against time and against concentration. The choice between the two- and three-compartment models was based on Akaike's Information Criterion.[26]

Mean values (SD) of the steady-state volume of distribution (V_{ss}), mean residence time (MRT) and elimination half-life ($t_{1/2}$) were calculated from the individual parameter estimates by a procedure similar to that used for the model parameters.[24 25]

Bile concentration–time (midpoint of sampling interval) data obtained from the T-drain were analysed using the same technique. Since the aforementioned pharmacokinetic model does not apply to bile concentration and we were primarily interested in the terminal half-life of rocuronium in bile, the model was defined as a (multi) exponential equation.

Statistical analysis

Data were summarized as mean (SD) (range). When concomitant medication interfered with the assay, the relevant data generated after the administration of the interfering drug were eliminated from the data analysis. For patients participating in Part A, the bile, stoma, urine and total recovery data were summarized for up to 24 and 48 h wherever possible. Because of the descriptive aims of the study, no further statistical analysis was performed.

Results

The data for the total recovery of rocuronium and 17-desacetyl-rocuronium in urine, bile and faeces are summarized in Table 2.

Part A

Excretion into urine

The mean urinary recovery within 48 h after administration was 26% of the dose (Table 2). The recovery in patients receiving rocuronium 0.3 mg kg^{-1} was comparable to that in patients receiving 0.9 mg kg^{-1}.

Excretion into bile collected from T-drain

In 11 patients from whom bile was collected from the T-drain, the indications for surgery were cholelithiasis (*n*=2), ductus choledochus lesions (*n*=3), liver tumours (*n*=4), choledochal cyst (*n*=1) or hepatic cyst (*n*=1). The amounts of bile collected from the T-drains ranged from 149–822 ml (mean 493 ml). The mean recovery within 48 h after administration was 7% of the dose (Table 2).

Total excretion into urine and bile

Total excretion was calculated in those patients from whom evaluable urine and T-drain bile samples were available. The total percentage recovered was 34% of the dose (Table 2), of which up to 0.4% was 17-desacetyl-rocuronium. The amounts of 17-desacetyl-rocuronium recovered were of the same order of magnitude in all sample types tested.

Stoma fluid

The three patients from whom stoma fluid was collected underwent bowel surgery. The volume of stoma fluid amounted to 60, 455 and 313 ml respectively. The percentage of the rocuronium dose (0.3 mg kg^{-1}) recovered in stoma fluid was 0.04, 0.02 and 2.5% after 24 h and 0.04, 4.1 and 12.0% after 48 h in these three patients respectively. The amounts of 17-desacetyl-rocuronium in stoma fluid were very small, ranging from 0 to 0.13% of the dose.

Liver content

Liver tissue was obtained from four patients who underwent hemihepatectomy because of a liver tumour, between 2.3 and 5.1 h after administration of rocuronium 0.9 mg kg^{-1}. Assuming an even distribution of rocuronium, the livers were estimated to contain between 6.3 and 13.2% (mean 9.3%) of the injected dose as rocuronium and up to 0.11% as 17-desacetyl-rocuronium.

Concentration in bile sampled from common bile duct

In 10 patients who underwent laparoscopic surgery for cholelithiasis, two to four bile samples were taken between 27 and 70 min after administration of rocuronium 0.9 mg kg^{-1}. The rocuronium concentrations ranged between 2 and 1217 mg l^{-1} (median value 377 mg l^{-1}), and the ratio of simultaneous concentrations in bile and plasma ranged from 130 to 2800 (median ratio 400). The concentrations of metabolites were much lower, and amounted to between 0 and 2.1% (median value 1.2%) for 17-desacetyl-rocuronium, and between 0 and 0.24% (median value 0.06%) for *N*-desallyl-rocuronium, expressed as a percentage of the rocuronium concentration.

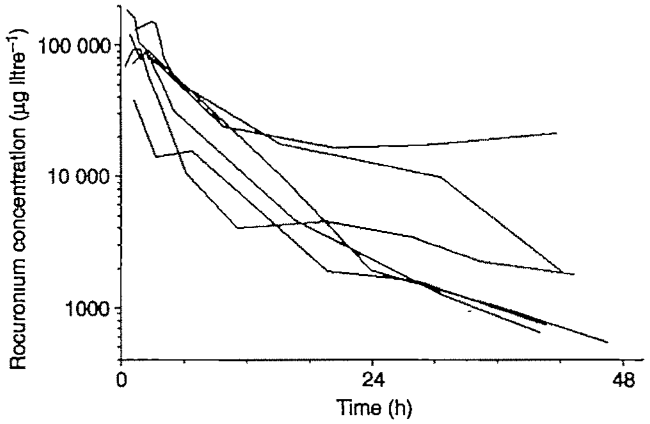

Fig 1 Semi-log plot of bile concentration profiles obtained from T-drain for each individual patient who received rocuronium 0.9 mg kg^{-1} (*n*=6)

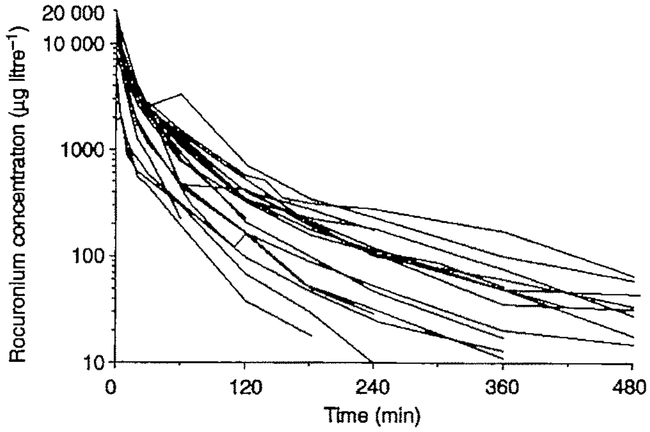

Fig 2 Semi-log plot of measured plasma concentration profiles for each individual patient (*n*=19). The two lower lines refer to the two patients who received rocuronium 0.3 mg kg^{-1}; the remaining lines refer to a 0.9 mg kg^{-1} dose.

Pharmacokinetic analysis of bile concentration data

A total of 51 bile samples from the T-drains were obtained from six patients receiving rocuronium 0.9 mg kg^{-1}. The measured bile concentration profiles for each individual patient are shown in Figure 1. Using the Iterative Two-Stage Bayesian analysis, a bi-exponential equation fitted the data significantly better than a mono-exponential equation. The mean (SD) (range) values for the two half-lives were 2.3 (0.7) h (1.6–2.8 h) and 16 (11) h (10–44 h) respectively.

Pharmacokinetic analysis of plasma concentration data

Plasma samples were obtained from 17 patients receiving rocuronium 0.9 mg kg^{-1} and from two patients receiving 0.3 mg kg^{-1} (a total of 218 samples). The measured plasma concentration profiles for each individual patient are shown in Figure 2. Using the Iterative Two-Stage Bayesian analysis, a three-compartment model fitted the data significantly better than a two-compartment model. Since the parameters of the two patients receiving the 0.3-mg kg^{-1} dose were within the range of values in the group receiving

0.9 mg kg^{-1}, the data of both dose groups were analysed together. The following values (mean (SD); n=19) were obtained: CL 3.7 (1.2) ml kg^{-1} min^{-1}, V_1 58 (15) ml kg^{-1}, CL_{12} 7.0 (1.5) ml kg^{-1} min^{-1}, V_2 58 (20) ml kg^{-1}, CL_{13} 0.79 (0.30) ml kg^{-1} min^{-1}, V_2 102 (36) ml kg^{-1}, V_{ss} 223 (43) ml kg^{-1}, MRT 60 (20) min, and elimination $t_{1/2}$ 115 (27) min. The residual coefficient of variation was 14%.

In six patients, low levels of 17-desacetyl-rocuronium were detected immediately following administration of rocuronium, rapidly decreasing to levels below the detection limit.

Part B

Excretion into urine

In Part B, urine was collected from 10 patients for up to 4–8 days after surgery. After 3 days the urinary excretion rates of rocuronium and metabolites were very low. The mean percentage of rocuronium recovered from urine was 27% of the administered dose (Table 2). The amounts of 17-desacetyl-rocuronium recovered in urine were small, ranging from 0 to 0.5% of the dose of rocuronium.

Excretion into faeces

The number of stools during the study period varied between patients from one to six, collected up to 7 days after surgery. In three patients the scheduled collection period of 7 days could not be completed since they left hospital earlier than anticipated. In these three patients the faecal recovery of rocuronium was not lower than in the remaining seven patients. These patients were therefore included in the analysis. The mean percentage of rocuronium recovered from faeces was 31% of the dose (Table 2). The amounts of 17-desacetyl-rocuronium recovered in faeces were small, ranging from 0 to 2.4% of the administered dose of rocuronium.

Total excretion into urine and faeces

The mean total excretion into urine and faeces was 58% of the dose (Table 2). In four out of 10 patients, the total recovery exceeded 80% of the administered dose of rocuronium.

Discussion

This study was performed in order to evaluate the relative contributions of the various excretion pathways of rocuronium and its potential metabolites in man. In Part A, all feasible techniques for bile collection in routine practice were employed: collection from T-drains, sampling by direct puncture of the common bile duct and collection of stoma fluid. In addition, the urinary excretion and the concentration in plasma and liver tissue were measured. This necessitated performing the study in various types of patients and at several locations. In Part B, the recovery of rocuronium and its metabolites in urine and faeces was determined.

The pharmacokinetic parameters of a three-compartment model obtained from plasma data were in good agreement with those reported previously,[3–18] indicating that the population of patients participating in this study was representative of those usually enrolled in pharmacokinetic studies of rocuronium and other neuromuscular blocking agents.

The recovery of rocuronium from bile collected from the T-drain ranged from 0.5 to 21.5% of the dose, with a mean value of 6.9%. In a similar study, Bencini and colleagues reported a recovery of 11% (range 2–18%) for vecuronium.[21] The biliary recovery may be underestimated in this study for the several reasons. First, the mean amount of bile collected in 48 h was 493 ml. This is about 50% of the normal bile production of 500–600 ml day^{-1}.[27 28] This small quantity of bile obtained from T-drains could be related to the fact that four out of the six patients receiving rocuronium 0.9 mg kg^{-1}, and with evaluable T-drain samples, underwent hemihepatectomy for a hepatic tumour. Immediately after liver resection, drug clearance by the liver may be reduced and bile production and the biliary excretion of rocuronium may be decreased. Second, an unknown fraction of bile may have reached the bowel instead of leaving the body via the T-drain during the surgical procedure. Third, bile could be collected for only 2 days in patients who were fed parenterally and little was produced. It is, therefore, likely that the biliary excretion of rocuronium was underestimated in this study.

Stoma samples could be collected for only 48 h postoperatively. In the three patients from whom evaluable stoma samples were obtained, a large variability was observed in the volumes produced during this period. This may be explained by the post-operative fasting regime. In the presence of an ileostomy, smaller volumes of stoma fluid will be produced, depending on the duration and type of the fasting regime. Moreover, during that postoperative fasting period, there is no stimulus for bile to be secreted. It is, therefore, likely that the excretion by this route was also underestimated in our study.

Liver tissue was obtained from four patients. For the calculation of the rocuronium content of liver tissue specimens, the individual total liver mass was estimated by the surgeon during the operation. Further, it was assumed that rocuronium was evenly distributed throughout the liver. This assumption may be flawed due to possible uneven or changing blood flow within the liver. Since the liver tissue sections were taken from the tumorous part of the liver, it cannot be excluded that the rocuronium contents in the examined sections underestimated the contents in healthy parts of the liver. In addition, the results may be further underestimated by incomplete extraction of rocuronium during the analytical procedure.

A large variation in total urinary rocuronium excretion was seen between patients, with recovery percentages ranging from 12 to 60%. In all patients, the highest rocuronium concentration was observed in the first urine samples. After 24 h, rocuronium concentrations in the urine were very low. The urinary recovery of rocuronium was consistent in Parts A and B. These urinary recovery results are also consistent with those reported earlier for rocuronium. Wierda and colleagues reported a mean cumulative urinary excretion of 33% of the administered dose during the first 12 h.[3] Alvarez-Gomez and colleagues and Van den Broek and colleagues observed a mean cumulative urinary excretion of 18%, and of 12–22% of the administered dose within 12 h, respectively.[7,8] As in the present study, the major part of rocuronium was excreted within the first 2 h after administration. The urinary recovery of rocuronium is comparable with that of vecuronium. Bencini and colleagues reported a urinary recovery of 30% of vecuronium, including 10% of the dose as the 3-desacetyl metabolite.[32]

In Part B of the study, a total recovery of more than 80% of the administered dose was observed within 7 days in four out of 10 patients, suggesting that rocuronium may eventually be completely eliminated via the renal and biliary routes. The fact that in six patients a total recovery of less than 60% was observed may be explained in part by the clinical setting in which the study was performed. It is possible that recovery of the compound might have been higher if all patients had stayed in hospital for a prolonged period to allow samples to be collected. As the patients were in bed and sometimes received opioids for pain management, they had irregular stools. Only one or two faecal samples were collected from some patients, which could have resulted in an erroneously low recovery percentage, as at least part of this stool was probably already in the bowel at the time rocuronium was administered. Indeed, in most cases a small percentage of the administered dose was found in the first stool.

The minimal amounts of 17-desacetyl rocuronium detected were mainly excreted in the earlier fractions of bile and urine, which is consistent with findings in the rat and dog (unpublished observations, Organon Teknika). The compound 17-desacetyl rocuronium was present in the ampoules at levels of up to 2% at batch release and at levels of up to 4% at the expiry date. It is, therefore, likely that the amounts of this compound detected were administered rather than the result of *in vivo* biotransformation. *N*-desallyl-rocuronium was found in very small amounts only in bile samples collected from the common bile duct. It is not unlikely that these minute amounts were also present in the ampoules or were formed during analysis, rather than resulting from *in vivo* biotransformation.

Although there are no indications of the presence of unknown derivatives of rocuronium in the present study, it cannot be excluded that rocuronium is excreted into urine and/or bile in the form of as yet unknown metabolites (e.g. conjugated to glucuronic acid or sulphate) which were not detected by the analytic technique used. It is also possible that biotransformation of rocuronium occurs by the faecal flora and/or by the alkaline climate of the intestines, although in the present study there were no indications to substantiate this. This may be the reason for not being able to account for all of the rocuronium.

The pharmacokinetic analysis of the bile concentration data from the T-drains revealed a bi-exponential decay with $t_{1/2}$ of 2.3 and 16 h respectively. The first half-life agrees well with the terminal half-life in plasma; the second half-life is much longer. This may indicate that a similar terminal half-life exists in plasma but is not observed because it occurs either at concentrations below the limit of quantification, or after the last sampling time. However, in the case of prolonged administration of rocuronium, this longer half-life will become apparent. In two studies in intensive care patients, the mean terminal half-life after infusion of rocuronium for 1–2 days was 6–24 h in patients with multi-organ failure.[29,30] The longer terminal half-life observed after prolonged administration demonstrates that the volume of distribution at steady-state is much higher than the value obtained in single-dose studies.[29]

The rocuronium concentrations in bile sampled directly from the common bile duct were much higher than the simultaneous plasma concentration, and in most cases even exceeding the plasma concentration shortly after administration. This finding reflects the efficiency of the biliary excretion of rocuronium in man, as was found earlier in animal experiments,[1,2,33] and suggests that an active carrier-mediated transport process is involved.[31]

In conclusion, the results of this study demonstrate that rocuronium is taken up by the liver and excreted into bile in very high concentrations. The amount of rocuronium excreted within 7 days into urine and faeces was 26 and 30% of the administered dose respectively, including small amounts of 17-desacetyl-rocuronium. The total recovery was on average 58%, and ranged from 16 to 100% of the administered dose.

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Rapacuronium 2.0 or 2.5 mg kg^{-1} for rapid-sequence induction: comparison with succinylcholine 1.0 mg kg^{-1}

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The purpose of this nine-centre study in 602 patients was to show that the frequency of acceptable intubating conditions after rapacuronium 2.0 or 2.5 mg kg^{-1} is not more than 10% lower than the frequency after succinylcholine 1.0 mg kg^{-1} during rapid-sequence induction of anaesthesia with fentanyl 1–2 μg kg^{-1} and thiopental 2–7 mg kg^{-1}. Laryngoscopy and intubation were carried out 60 s after administration of muscle relaxant by an anaesthetist blinded to its identity. Intubating conditions were clinically acceptable (excellent or good) in 91.8% of patients given succinylcholine and in 84.1 and 87.6% of patients given rapacuronium 2.0 and 2.5 mg kg^{-1} respectively. With respect to the percentage of clinically acceptable intubating conditions, the estimated difference (and the upper limit of the one-sided 97.5% confidence interval) between succinylcholine and rapacuronium 2.0 mg kg^{-1} was 7.8 (14.4)% and between succinylcholine and rapacuronium 2.5 mg kg^{-1} it was 4.0 (10.2)%. For both comparisons, the upper limit of the one-sided confidence interval exceeded the predefined 10% difference. Hence, it could not be demonstrated that the intubating conditions with either of the two doses of rapacuronium were not inferior to those with succinylcholine 1.0 mg kg^{-1}. The increase in heart rate was significantly greater during the first 5 min in the rapacuronium groups, but the arterial pressure increased significantly only in the succinylcholine group ($P<0.001$). Respiratory side-effects were observed in 4.0, 13.5 and 18.5% of patients after succinylcholine and rapacuronium 2.0 and 2.5 mg kg^{-1} respectively ($P<0.05$). As the non-inferiority of intubating conditions after rapacuronium 2.0 and 2.5 mg kg^{-1} could not be proven, succinylcholine should be considered the neuromuscular blocking agent that provides better intubating conditions for rapid-sequence induction.

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Keywords: anaesthesia, rapid sequence induction; anaesthesia, intubation; neuromuscular block, rapacuronium; neuromuscular block, succinylcholine

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Although succinylcholine has been considered to be the neuromuscular blocking drug of choice for facilitating intubation during rapid-sequence induction, its use can be associated with a large number of side-effects.[1 2] Studies using the rapid-onset, non-depolarizing neuromuscular blocking drug rocuronium have shown that it provides a frequency of acceptable intubations similar to that given by succinylcholine, but its duration of action is too long to allow early reversal.[3–7]

Rapacuronium is a non-depolarizing neuromuscular blocking agent with the characteristics of rapid onset, short duration of action and the feasibility of early

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antagonism.[8] It may be a safe and effective alternative to succinylcholine for facilitating tracheal intubation during rapid-sequence induction of anaesthesia. In a previous study, clinically acceptable intubating conditions were achieved significantly less frequently after rapacuronium 1.5 mg kg^{-1} (89.4%) than after succinylcholine 1.0 mg kg^{-1} (97.4%) during rapid-sequence induction of anaesthesia.[9] Increasing the initial dose of a neuromuscular blocking agent is commonly used to shorten onset time and to improve intubating conditions.[5 10 11] The results of a dose-finding study suggest that using higher doses of rapacuronium (2.0 or 2.5 mg kg^{-1}) results in a more rapid onset and may result in a higher number of excellent and good tracheal intubating conditions.[12]

The aim of the present study was to compare the intubating conditions during rapid-sequence induction after rapacuronium 2.0 and 2.5 mg kg^{-1} with the conditions after succinylcholine 1.0 mg kg^{-1}. As equivalence was not expected,[9] based on a comparison between rapacuronium 1.5 mg kg^{-1} and succinylcholine 1.0 mg kg^{-1}, the aim of the study was to prove non-inferiority of these two doses of rapacuronium compared with a standard dose of succinylcholine (see Appendix). In addition, adverse events and the cardiovascular response to induction of anaesthesia and intubation were assessed.

Patients and methods

Six hundred and two adult patients (ASA I–III, body mass index <35) scheduled for surgery under general anaesthesia were enrolled in the study with their informed consent and approval of the ethics committees of the nine participating study centres. Patients were randomly assigned to receive succinylcholine 1 mg kg^{-1} or rapacuronium 2.0 or 2.5 mg kg^{-1}. A separate randomization was used for each centre and was stratified to include 80% adult and 20% elderly (>65 yr) subjects. Patients requiring rapid-sequence induction were also to be included whenever feasible. Patients with expected difficult intubation, a history of malignant hyperthermia or taking medication known to interact with neuromuscular blocking agents and pregnant patients were excluded. Any history of bronchial hyperreactivity (allergy-induced, exercise-induced and/or cold-induced asthma) and smoking was noted. Patients were not allowed sedatives within 8 h or opioids within 2 h of anaesthesia.

After fentanyl 1–2 µg kg^{-1} and 3 min of preoxygenation, anaesthesia was induced with thiopental 2–7 mg kg^{-1} followed by the neuromuscular blocking drug. Fentanyl and thiopental doses were decided by the anaesthetist within defined ranges, according to the weight and clinical condition of the individual patient. All drugs were injected into a rapidly running infusion of lactated Ringer's solution, the neuromuscular blocking drugs being injected within 5 s. Cricoid pressure was applied after loss of consciousness.

Tracheal intubation was carried out by an experienced anaesthetist who was blinded to the identity of the neuromuscular blocking drug (by remaining outside the room for 45 s after its administration). Laryngoscopy and intubation, including cuff inflation, were commenced 60 (±5) s after completion of injection of the neuromuscular blocking drug and had to be completed within 20 s. Intubating conditions were evaluated according to a standard scheme in which assessments were made of the ease of laryngoscopy, the position and movement of the vocal cords, and coughing and limb movement on insertion of the tracheal tube.[13] Each variable was graded as excellent, good or poor, or not applicable if it could not be assessed. The overall intubating conditions were classified as excellent (all variables scored as excellent), good (at least one of the variables scored as good but none scored as poor) or poor (at least one variable scored as poor). Excellent or good conditions were considered clinically acceptable.

Anaesthesia for the first 5 min after intubation was maintained with 66% nitrous oxide in oxygen and isoflurane (up to 1% inspired). Heart rate, non-invasive arterial blood pressure and arterial oxygen saturation were assessed in all patients during the preoxygenation period (baseline) and 2, 3, 4 and 5 min after administration of the neuromuscular blocking agent. The study terminated at this point and anaesthesia thereafter was managed as appropriate.

Note was made of any adverse events during the intra- or postoperative periods. An adverse event was defined as an unusual or unexpected sign which manifested itself or worsened during the study and post-study periods. According to the principles of good clinical practice, the anaesthetist decided on the existence, severity and drug-relatedness of any adverse event. Particular attention was paid to skin reactions and respiratory side-effects, such as bronchospasm, increased airway pressure, wheezing on auscultation and oxygen desaturation below 95%.

The primary efficacy variable of the study was the intubating condition 60 s after injecting the neuromuscular blocking agent (clinically acceptable versus unacceptable). Non-inferiority of the intubating conditions for each dose of rapacuronium was determined in comparison with succinylcholine. The concept of non-inferiority (see Appendix)[14] was used, as it was expected from the results of previous studies[9 12] with rapacuronium that the conditions after rapacuronium would be slightly worse than those after succinylcholine. With respect to clinically acceptable intubating conditions, rapacuronium was considered to be not inferior to succinylcholine in cases where the percentage of clinically acceptable intubating conditions after rapacuronium was not more than 10% lower than the percentage after succinylcholine. Thus, the null hypothesis was defined to be $P_{rap}<P_{sux}-10\%$, and the alternative hypothesis to be $P_{rap}>P_{sux}-10\%$, where P_{rap} and P_{sux} are the percentages of clinically acceptable intubating conditions after rapacuronium and succinylcholine respectively.

To determine if each of the two doses of rapacuronium was not inferior to succinylcholine 1.0 mg kg^{-1}, each of the rapacuronium dose groups was tested against the succinylcholine group separately. For each of the two statistical tests, the probability of falsely claiming non-inferiority was 0.05/2 (to allow for two comparisons). To test this null hypothesis, a one-sided 97.5% confidence interval was calculated for the difference between succinylcholine and rapacuronium. The null hypothesis of inferiority was rejected in favour of the alternative hypothesis of non-inferiority when the upper limit of this one-sided 97.5% confidence interval did not exceed 10%, a difference of this size between the two neuromuscular blocking drugs being considered clinically irrelevant. An estimate of the difference in the frequency of acceptable intubating conditions between two treatment groups was calculated as follows. For each trial site, the difference in the frequency of acceptable intubating conditions was estimated separately, and the overall treatment difference was calculated by averaging these estimates using the number of subjects per trial site as a weighting factor (see Appendix). Any influence of the dosage of induction agents used, age and any centre effect was also assessed, using a logistic regression model.

Sample size calculations were based on an estimated frequency of clinically acceptable intubating conditions of 97% after succinylcholine 1.0 mg kg^{-1} and 94% after rapacuronium. This required 184 patients in each of the three groups of the study to have a power of 90%.[15] It was planned that 200 subjects should be enrolled in each group to allow for unevaluable patients.

Safety variables (cardiovascular response and adverse events) were evaluated on the basis of data of all patients receiving the neuromuscular blocking drugs. Repeated measures analysis of variance was performed with each cardiovascular variable (heart rate, mean arterial pressure) as the dependent variable, the respective baseline value as the covariable and the time of assessment, treatment group and their interaction term as independent factors. A significant interaction would indicate differences in the cardiovascular response to the neuromuscular blocking drug used. The incidence of adverse events was compared between groups using the χ^2 test. Significant differences were assumed if χ^2 exceeded 5.02389 ($\alpha = 0.05/2$, to allow for two comparisons). Logistic regression analyses were performed with respiratory side-effects as the dependent variable, treatment group as the covariable and the existence of a medical history of bronchial hyper-reactivity or smoking, and the study centre (and the respective interaction terms) as independent factors. The forwards stepwise method was used for selection of the relevant variables in the model.

Results

Two patients were withdrawn from the study before administration of the neuromuscular blocking drug, because of the presence of cardiac arrhythmia after induction of anaesthesia in one patient and the inadvertent administration of a benzodiazepine preoperatively in the other; 600 patients (292 males and 308 females) therefore received the study medication. The groups were comparable with regard to age, weight, height and sex distribution (Table 1).

Table 1 Patient characteristics (mean (SD) (range))

	Succinylcholine 1.0 mg kg^{-1} (*n*=200)	**Rapacuronium 2.0 mg kg^{-1} (*n*=200)**	**Rapacuronium 2.5 mg kg^{-1} (*n*=200)**
Age (yr)	47 (16)	49 (16)	47 (17)
	(19–87)	(18–84)	(16–83)
Weight (kg)	73 (13)	74 (14)	73 (13)
	(40–115)	(45–130)	(42–113)
Height (cm)	170 (10)	171 (10)	169 (10)
	(147–201)	(144–196)	(148–198)
Male female	100 100	104·96	88 112

Table 2 Frequency distribution of the intubating conditions at 60 s, 538 observations (*n* (%))

	Succinylcholine 1.0 mg kg^{-1} (*n*=184)	**Rapacuronium 2.0 mg kg^{-1} (*n*=176)**	**Rapacuronium 2.5 mg kg^{-1} (*n*=178)**
Excellent	115 (62.5%)	93 (52 8%)	112 (62.9%)
Good	54 (29.3%)	55 (31.3%)	44 (24.7%)
Poor	8 (4 3%)	15 (8.5%)	12 (6 7%)
Impossible	7 (3 8%)	13 (7 4%)	10 (5.6%)
Acceptable	169 (91.8%)	148 (84 1%)	156 (87 6%)
Not acceptable	15 (8.2%)	28 (15 9%)	22 (12.4%)

Intubation data were excluded from 62 patients because of protocol violations such as age below 18 yr, allocation to a wrong group, the dose of fentanyl, thiopental or neuromuscular blocking drug deviating by more than 10% from that specified in the protocol, administration of sedatives or opioids during the prestudy period, withdrawal from the study before the intubating conditions had been scored, and failure to complete the time schedule for drug administration or intubation. The intubating conditions are therefore presented for 538 patients (Table 2). There were 149 and 35, 142 and 34, and 141 and 37 adult and elderly subjects respectively in the succinylcholine and rapacuronium 2.0 and 2.5 mg kg^{-1} per-protocol groups respectively. The conditions were acceptable (excellent or good) in 91.8, 84.1 and 87.6% of patients in the three groups respectively. With respect to the percentage of clinically acceptable intubating conditions, the estimated difference (and the upper limit of the one-sided 97.5% confidence interval) between the succinylcholine and the rapacuronium 2.0 mg kg^{-1} group was 7.8 (14.4)% and that between the succinylcholine and the rapacuronium 2.5 mg kg^{-1} group was 4.0 (10.2)%. For both comparisons, the upper limit of the one-sided confidence interval exceeded the 10% that had been defined as indicating a clinically irrelevant difference

Table 3 Frequency distribution of variables contributing to poor intubating conditions (n=35). Intubation was impossible in an additional 30 patients, mostly because of impossible laryngoscopy or closed vocal cords (some patients had more than one factor present) *P<0.05 compared with succinylcholine 1 0 mg kg^{-1}

	Succinylcholine 1.0 mg kg^{-1} (n=8)	**Rapacuronium 2.0 mg kg^{-1} (n=15)**	**Rapacuronium 2.5 mg kg^{-1} (n=12)**
Difficult laryngoscopy	3	6	3
Closing vocal cords	2	11*	5
Moving vocal cords	2	3	2
Sustained coughing	3	7	5
Vigorous limb movement	0	2	1

in the percentage of clinically acceptable intubating conditions. Hence, it could not be demonstrated that the two doses of rapacuronium were not inferior to succinylcholine 1.0 mg kg^{-1}.

Clinically acceptable intubating conditions in patients requiring rapid-sequence induction (n=109) were observed in 32 of 36 (88.9%), 28 of 34 (82.4%) and 33 of 39 (84.6%) patients in the succinylcholine 1.0 mg kg^{-1} and rapacuronium 2.0 and 2.5 mg kg^{-1} groups respectively. Intubating conditions in the elderly were similar to those in the whole population.

Logistic regression analysis revealed no effect of the dose of fentanyl, the dose of thiopental or age group on intubating conditions, but a centre effect was present. The percentage of acceptable intubating conditions at the different centres ranged from 83 to 100 for succinylcholine, from 67 to 100 for rapacuronium 2.0 mg kg^{-1} and from 71 to 100 for rapacuronium 2.5 mg kg^{-1}. The reasons for non-acceptable intubating conditions are given in Table 3, the most common being closing of the vocal cords. Impossible laryngoscopy or closed vocal cords were the reasons for failed intubation.

Repeated measures analysis of variance showed that heart rate increased more during the first 5 min in the rapacuronium groups, whereas the mean arterial pressure was increased only in the succinylcholine group (P<0.01; Fig. 1). The incidence of adverse events is given in Table 4. Of particular note was the high incidence of adverse respiratory effects, which occurred more frequently after rapacuronium. The incidence of respiratory side-effects differed between the three treatment groups and between smokers and non-smokers (P=0.0012). The incidence was higher in smokers than in non-smokers. Respiratory side-effects also appeared to be more common in patients with bronchial hyper-reactivity and those receiving rapacuronium. Respiratory side-effects showed a centre-related incidence (P=0.003), varying from 0 to 12% for succinylcholine, from 0 to 27% for rapacuronium 2.0 mg kg^{-1} and from 0 to 36% for rapacuronium 2.5 mg kg^{-1}.

Three serious adverse events were observed in the 600 patients receiving the study drugs. One patient receiving rapacuronium 2.0 mg kg^{-1} experienced severe bronchospasm and oxygen desaturation, which was probably related to rapacuronium. The patient recovered completely but required a β-agonist drug by inhalation. Another patient receiving rapacuronium 2.5 mg kg^{-1} bled on the second postoperative day, which resulted in prolonged hospitalization, but ultimately made a full recovery. A third patient receiving rapacuronium 2.5 mg kg^{-1} died as a result of multi-organ failure. The complications in the last two patients were not considered to be rapacuronium-related.

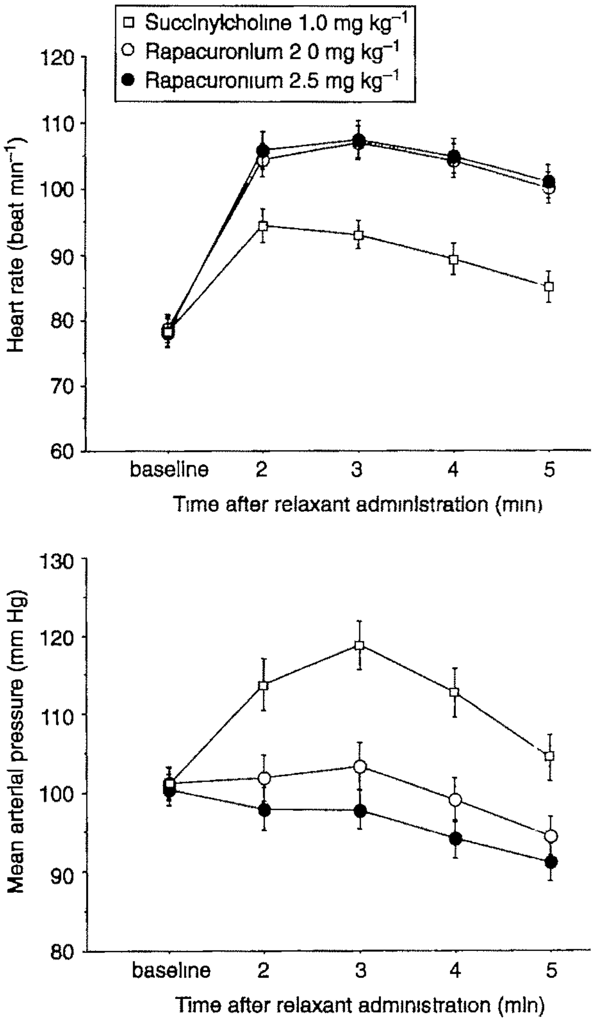

Fig 1 Heart rate and mean arterial pressure (n=600). Mean and 95% confidence intervals For both variables, responses to succinylcholine 1 0 mg kg^{-1} (open squares) were significantly different from responses to rapacuronium 2 0 mg kg^{-1} (open circles) and 2.5 mg kg^{-1} (filled circles). P<0 01 for the interaction term between treatment group and time of assessment

Discussion

The present study was performed because a previous study had shown that rapacuronium 1.5 mg kg^{-1} did not provide acceptable intubating conditions as often as succinylcholine 1.0 mg kg^{-1}.[9] However, this nine-centre, European,

Table 4 Adverse events (n=600). *P<0.05 compared with succinylcholine 1.0 mg kg^{-1}. **Incidence of respiratory side-effects was significantly higher in smokers receiving rapacuronium (logistic regression analysis P=0.0012 for smoking, P<0.0001 for group)

	Succinylcholine 1.0 mg kg^{-1} (n=200)	**Rapacuronium 2.0 mg kg^{-1} (n=200)**	**Rapacuronium 2.5 mg kg^{-1} (n=200)**
Respiratory side-effects	7 (3.5%)	27 (13.5%)*	37 (18.5%)*
With history of smoking**			
Smokers	6/99 (6.1%)	13/84 (15.7%)	23/88 (23.8%)
Non-smokers	1/101 (1.0%)	14/116 (12.0%)	14/112 (11.6%)
With bronchial hyper-reactivity			
Yes	0/16 (0%)	4/17 (28.6%)	3/17 (20.0%)
No	7/184 (3.8%)	23/183 (12.4%)	34/183 (18.3%)
Skin reactions	20 (10.0%)	26 (13.0%)	34 (17.0%)
Adverse events			
Total	52 (26.0%)	67 (33.5%)	77 (38.5%)
Possibly drug-related	32 (16.0%)	53 (26.5%)	64 (32.0%)*

randomized, assessor-blinded study could not show that intubating conditions in rapid-sequence induction are not inferior even with rapacuronium 2.0 or 2.5 mg kg^{-1}. This was in spite of the fact that laryngoscopy and intubation were carried out in the present study at 60 s compared with 50 s in the previous study.

From the results of a dose-finding study by Kahwaji and colleagues,[12] it was expected that an increase in the dose of rapacuronium to 2.0 or 2.5 mg kg^{-1} would result in an increase in the frequency of acceptable tracheal intubating conditions that were similar to or only slightly (<10%) worse than those after succinylcholine. Therefore, this clinical trial was designed to show that the conditions obtained with the doses of rapacuronium used in the present study would not be inferior to those obtained with succinylcholine 1.0 mg kg^{-1}. For such a study design, the statistical methods used to detect differences between two treatments are not appropriate (see Appendix). Thus, a statistical method was chosen which was based on the confidence interval approach. Since we wanted to prove that the intubating conditions after each of the two doses of rapacuronium were not inferior to those after succinylcholine 1.0 mg kg^{-1}, one-sided confidence intervals were used. This made it necessary to decide a limit for assuming non-inferiority in intubating conditions, which was fixed at 10% in our study. Others may consider such a difference to be too large; Goulden and Hunter stated that '... most anaesthetists would, if possible, select excellence...' for intubating conditions for rapid-sequence induction.[16] Because the non-inferiority of rapacuronium 2.0 and 2.5 mg kg^{-1} could not be proven within this limit in our study, succinylcholine should be considered the neuromuscular blocking agent that provides better intubating conditions in a rapid-sequence induction setting, when compared with rapacuronium in the doses used here.

Clinically acceptable intubating conditions were present in 91.8% of patients after succinylcholine 1.0 mg kg^{-1} in the present study. This was lower than the 97.0 and 96.9% reported in two recent studies comparing succinylcholine with rocuronium or rapacuronium, in which some of the present investigators were involved.[3 9] However, it is difficult to compare intubating conditions from different studies because of variation in the protocols. This becomes more obvious when considering American[17] and European[9] studies, in both of which the intubating conditions were compared after succinylcholine 1.0 mg kg^{-1} and rapacuronium 1.5 mg kg^{-1}. Although the patients in the American study were probably intubated under deeper anaesthesia, the rate of acceptable intubating conditions was 2–3% lower in both groups of the American study.

Depth of anaesthesia affects the quality of intubation conditions, as shown by previous studies with rocuronium in which a dose that provided acceptable intubating conditions under stable anaesthesia was found to be inadequate when administered under the conditions of rapid-sequence induction.[3 18] In the present study, patients received no sedative premedication and anaesthesia was induced with thiopental and fentanyl in relatively small doses, in order to carry out a typical rapid-sequence induction. This technique (using relatively light anaesthesia) may have contributed to the overall slightly lower incidence of acceptable intubating conditions.

The higher frequency of non-acceptable intubating conditions in the rapacuronium groups may have resulted from incomplete neuromuscular block in the laryngeal muscles, as the vocal cords were closed more often in patients receiving rapacuronium. Previous studies with other neuromuscular blocking drugs such as vecuronium and rocuronium have demonstrated relative resistance but earlier onset of block in the muscles of the vocal cords compared with the adductor pollicis.[19 20] One study has shown similar results for rapacuronium.[21] Two recent studies, however, challenge the concept of the relative resistance of the laryngeal muscles and shorter onset times of neuromuscular blocking drugs in laryngeal compared with peripheral muscles. D'Honneur and colleagues were unable to demonstrate differences between onset times in laryngeal and peripheral muscles for rocuronium and succinylcholine[22], and Wright and colleagues were unable to do so for rapacuronium.[23] The latter authors explained the rapid onset of rapacuronium by the rapid equilibration between concentrations in the plasma and at the effect site.[23] This may indicate the need for doses of rapacuronium larger than those used in the present study, or for more time to elapse so that a better quality of block can develop in the laryngeal muscles.

It is possible that the doses of rapacuronium used in the present study were less potent than the dose of succinylcholine used. Information about the potency of rapacuronium is very sparse. Using electromyography, Kahwaji and colleagues reported maximum blocks of 57, 91 and 98% with rapacuronium 0.5, 1.0 and 1.5 mg kg^{-1} respectively.[12] Debaene and colleagues, using mechanomyography, reported maximum blocks of 94, 97 and 99% respectively with rapacuronium 0.75, 1.5 and 2.0 mg kg^{-1}.[21] Regression analysis of these data (carried out by the authors of the present study) yielded ED_{95} values of approximately 1.16 and 0.90 mg kg^{-1} respectively. Thus, the doses of rapacuronium used in the present study were approximately 2.0 and 2.5 times its ED_{95}, whereas the dose of succinylcholine used, 1.0 mg kg^{-1}, is just under four times the ED_{95}.[24]

Increasing the dose of rapacuronium beyond those used in the present study would undoubtedly result in a further increase in the incidence of side-effects. The frequency of pulmonary side-effects of 18.5% that we found with rapacuronium 2.5 mg kg^{-1} would be considered unacceptable. In addition, we observed a significant increase in the heart rate in both the rapacuronium groups. Taken in conjunction with the study of Sparr and colleagues[9], the frequencies of respiratory side-effects of 10.7, 13.5 and 18.5% after rapacuronium 1.5, 2.0 and 2.5 mg kg^{-1} respectively indicates a dose-related effect. Another disadvantage of using larger doses of rapacuronium is the longer time it will take to antagonize the block.[25]

Respiratory complications such as bronchospasm, wheezing and increased airway pressure are of obvious concern, but their cause cannot be determined from the present study. Their occurrence along with erythema and an increase in heart rate may indicate histamine release. Their frequency is dose-related and there is some evidence of a dose-related increase in histamine levels after the administration of rapacuronium.[26] They may also be related to the technique of induction of anaesthesia or to predisposing factors in the patient. Fleming and colleagues, who did not perform a rapid-sequence induction technique, reported an incidence of bronchospasm of only 3.6 and 1.2% after administration of rapacuronium 1.5 mg kg^{-1} and succinylcholine 1.0 mg kg^{-1} respectively.[17] Our results also show that such untoward respiratory effects are more likely to occur in patients with a history of smoking and a tendency to bronchial hyper-reactivity.

In conclusion, the side-effects of succinylcholine make it desirable to have a non-depolarizing relaxant which provides good intubating conditions rapidly. Rapacuronium in the doses used in this study was shown not to be as good as succinylcholine, and the higher dose was associated with significant side-effects. A range of 1.5–2.0 mg kg^{-1} may be safer with rapacuronium, but this drug does not induce intubating conditions as good as those obtained with succinylcholine.

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Appendix

Superiority, equivalence and non-inferiority trials

Clinical trials can be divided into three categories: superiority, equivalence and non-inferiority trials. The choice of the trial depends on the objective of the trial. In a superiority trial the objective is to detect a difference between two treatments, or in other words to show that one treatment is superior to the other. For such a trial the null hypothesis is defined as 'there is no difference between the two groups', while the alternative hypothesis is 'there is a difference between the two groups'. The objective of an equivalence trial is to show that the response to two treatments differs by an amount which is considered clinically unimportant. A non-inferiority trial is designed to show that the response to the new treatment is not clinically inferior to a comparative agent, or in other words is not worse by a clinically important amount.

It is important to emphasize that absolute equivalence can never be demonstrated: it is possible only to assert that the true difference is unlikely to be outside a predefined interval, say $(-\delta, \delta)$. The limits of this interval should be chosen so that differences smaller than these values are considered not clinically relevant.

Statistical testing for equivalence or non-inferiority is generally based on the use of confidence intervals. A confidence interval defines a range for the possible true differences between the treatments. If every point within this interval corresponds to a difference of no clinical importance, then the treatments may be considered to be equivalent or one treatment is considered not to be inferior to the other.

For equivalence trials, it is important to use two-sided confidence intervals. If the predefined range of equivalence is defined as the interval from $-\delta$ to $+\delta$, it is possible to check whether the confidence interval centred around the observed difference lies entirely between $-\delta$ and $+\delta$. If it does, equivalence is demonstrated; if not, equivalence cannot be claimed.

For non-inferiority trials, one-sided confidence intervals should be used to show that the experimental treatment is not worse than the reference treatment. Non-inferiority is inferred if the upper one-sided confidence limit for the difference between the experimental and the reference agent does not exceed δ. For a non-inferiority trial, the hypotheses are defined as follows:

H_0: $\mu_e<\mu_r-\delta$

H_a: $\mu_e>\mu_r-\delta$

where μ_e and μ_r are the test statistics in the experimental and reference groups respectively.

These null and alternative hypotheses are not equal to those used in superiority trials, in which one wants to show that one treatment is superior to the other one. For a superiority trial they are defined as:

H_0: $\mu_r - \mu_e = 0$
H_a: $\mu_r - \mu_e \neq 0$.

For testing of equivalence or non-inferiority, the usual significance tests cannot be used because they do not test the correct null hypothesis. Furthermore, one does not demonstrate equivalence by *not* rejecting the null hypothesis, because 'absence of evidence is not evidence of absence'. Not rejecting H_0 can, for instance, be the result of an underpowered study, because the number of subjects enrolled was too low or because the variability observed in the data was larger then expected. In both cases it will not, in general, be possible to draw meaningful conclusions from the trial.

Topic E9 of the international conference on harmonization, *Statistical principles for clinical trials*, states: 'Concluding equivalence or non-inferiority based on observing a non-significant test result of the null hypothesis that there is no difference between the investigational product and the active comparator is inappropriate.'[27]

On the basis of results obtained from previous studies, showing a lower frequency of acceptable intubating conditions with rapacuronium than with succinylcholine, it could not have been expected that the frequency with rapacuronium would be higher in the present study. Therefore, the objective of the present study was to show that the frequency of acceptable intubating conditions after rapacuronium was only slightly lower (more precisely, it was not more than 10% worse) than the frequency after succinylcholine. For statistical analysis, the objective of a study should be translated into the alternative hypothesis. Let P_{rap} and P_{sux} be the percentages of clinically acceptable (excellent or good) intubating conditions after rapacuronium and succinylcholine respectively. The alternative hypothesis is now H_1: $P_{\mathrm{rap}} > P_{\mathrm{sux}} - 10\%$. Consequently, the null hypothesis, which is the opposite of the alternative hypothesis, becomes: H_0: $P_{\mathrm{rap}} < P_{\mathrm{sux}} - 10\%$. In other words, a non-inferiority trial was called for.

Estimate and variance of the difference between two treatments

The present trial is a multi-centre trial in which nine centres participated. Within each centre, the subjects were allocated randomly to treatment group 1, 2 or 3. For each subject, the success (success/failure) of the treatment is recorded. Two comparisons were made: succinylcholine versus each of the doses of rapacuronium.

We were interested in the difference between the probability of success of treatment 1 and the probability of success of treatment 2. An unbiased estimate (Q) of this difference is:

$$Q = \frac{\sum_{i=1}^{C} \frac{n_{i1} \cdot n_{i2}}{n_{i1} + n_{i2}} \cdot \left(\frac{x_{i1}}{n_{i1}} - \frac{x_{i2}}{n_{i2}} \right)}{\sum_{i=1}^{C} \frac{n_{i1} \cdot n_{i2}}{n_{i1} + n_{i2}}}$$

where n_{ij} is the number of subjects in centre i receiving treatment j, and x_{ij} is the number of successful treatments in centre i receiving treatment j ($i=1,\ldots,C$, $j=1,2$, where C is the number of centres).

Using the Cochran–Mantel–Haenszel estimate, we can estimate $Var[Q]$ as

$$Var[Q] = \frac{\sum_{i=1}^{C} \frac{n_{i1} \cdot n_{i2}}{n_{i1} + n_{i2}} \cdot \frac{x_{i1} + x_{i2}}{(n_{i1} + n_{i2} - 1)} \cdot \left(1 - \frac{x_{i1} + x_{i2}}{n_{i1} + n_{i2}} \right)}{\left(\sum_{i=1}^{C} \frac{n_{i1} \cdot n_{i2}}{n_{i1} + n_{i2}} \right)^2}$$

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Duration of exposure to sevoflurane affects dose–response relationship of vecuronium

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The purpose of this study was to quantify the relationship between the dose–response curve of vecuronium and duration of exposure to an end-tidal concentration of 1.7% sevoflurane in 67% nitrous oxide and oxygen. Forty adult patients, in groups of 10, were allocated randomly to receive vecuronium by a cumulative dose method at intervals of 15 min (group 15), 30 min (group 30), 60 min (group 60) or 90 min (group 90) after starting inhalation of sevoflurane. Neuromuscular function was monitored by acceleromyographic train-of-four (TOF) responses of the adductor pollicis muscle to ulnar nerve stimulation. Dose–response curves were constructed by least-squares regression analysis and the effective doses of vecuronium (ED_{50}, ED_{90} and ED_{95}) were estimated and compared between groups. Mean (SEM) ED_{50}, ED_{90} and ED_{95} were 16.8 (0.5), 32.6 (1.7) and 40.9 (2.4) μg kg^{-1}, respectively, in group 15; 10.6 (1.0), 20.8 (1.7) and 26.2 (2.2) μg kg^{-1}, respectively, in group 30; 11.2 (1.1), 21.7 (1.6) and 27.3 (1.8) μg kg^{-1}, respectively, in group 60; and 11.0 (1.1), 21.7 (1.6) and 27.5 (1.9) μg kg^{-1}, respectively, in group 90. The values obtained in group 15 were significantly higher than those in the other three groups ($P<0.05$). The results indicate that the duration of sevoflurane anaesthesia influences the dose–response of vecuronium and 30 min inhalation of 1.7% end-tidal concentration is sufficient to achieve a stable potentiating effect.

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It is well known that potent inhalational anaesthetics augment the effect of neuromuscular blocking agents (NMBAs) to variable degrees[1–4] and the interaction seems to be time-dependent.[5–8] Sevoflurane has a marked inhibitory effect on neuromuscular transmission[9] and has a low blood/gas and tissue/gas solubility.[10–12] There is therefore a possibility that onset and stabilization of sevoflurane-induced potentiation of NMBAs may be more rapid than with other inhalational anaesthetics, such as halothane, enflurane or isoflurane. However, insufficient data are available on this issue. The purpose of this study was to quantify the relationship between the dose–response of vecuronium and the duration of exposure to 1.7% sevoflurane in nitrous oxide/oxygen in adult patients.

Methods

After obtaining hospital Ethics Committee approval and written informed consent, we studied 40 patients of both genders, ASA I or II, aged 20–60 yr, undergoing minor elective ENT or orthopaedic surgical procedures. None of the patients had neuromuscular, hepatic or renal disease or were taking any drug known to interact with NMBAs. Patients whose body weight was ≥30% more or less than their ideal weight were excluded from the study.

All patients were premedicated with pethidine 50 mg and atropine 0.5 mg i.m. approximately 45 min before induction of anaesthesia. An intravenous infusion of Ringer's acetated solution was started and electrocardiogram, pulse oximeter and non-invasive arterial pressure were continuously monitored after arrival in the operating theatre. Anaesthesia was induced with fentanyl 2–4 μg kg^{-1} and propofol 2.0–2.5 mg kg^{-1}. After topical anaesthesia with lidocaine 2%, the patients' trachea was intubated without the use of an NMBA. Anaesthesia was maintained with an end-tidal concentration of 1.7% sevoflurane and 67% nitrous oxide in oxygen which was monitored throughout the study with an anaesthetic gas analyser (Capnomac Ultima; Datex,

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Helsinki, Finland). Additional fentanyl was administered as required. Ventilation was adjusted to keep end-tidal $P\text{CO}_2$ within the range 35–38 mm Hg. Oesophageal and skin temperature over the thenar muscles were kept above 35°C and 33°C respectively, with a heating mattress and cotton wool.

The patients were allocated at random using the sealed envelope method to receive vecuronium after 15, 30, 60 or 90 min exposure to sevoflurane (10 patients per group). At least 15 min before the administration of vecuronium, stimulation of the ulnar nerve was commenced at the wrist with square-wave supramaximal stimuli of 0.2 ms duration, delivered in a train-of -four (TOF) mode at 2 Hz every 15 s using a TOF guard (Organon Teknika NV, Turnhout, Belgium). The contraction of the ipsilateral adductor pollicis muscle was measured by accelerometry. When baseline neuromuscular responses had stablized, patients were given vecuronium by a cumulative dose technique. Vecuronium 10 μg kg^{-1} was administered repeatedly via a rapidly running infusion until 95% depression of the first twitch response (T_1) in each TOF sequence was achieved. Repeated doses were administered when stable responses, defined as three equal consecutive T_1 responses, had been obtained after the previous dose, or when no further depression of the T_1 response had been obtained for at least 5 min after the last dose. The individual dose–response relationship was examined by plotting the log dose against the logit transformation of T_1 depression relative to baseline. Regression lines were constructed by least-squares regression analysis and parallelism of the lines was determined between groups. The effective doses of vecuronium that depressed the amplitude of T_1 in each TOF sequence by 50%, 90% and 95% (ED_{50}, ED_{90} and ED_{95}, respectively) were calculated from the regression lines and compared between the groups.

Data are presented as mean (SD or SEM). Statistical analysis was performed using the Kruskal–Wallis test. A *P* value of <0.05 was considered statistically significant. If a significant *P* value was obtained, further group comparisons were made using Scheffe's *F*-test or Fisher's PLSD test.

Results

Patient characteristics did not differ among the four groups (Table 1). Each cumulative dose of vecuronium 10 μg kg^{-1} produced greater depression of T_1 in groups 30, 60 and 90 than in group 15. The mean (SEM) steepness coefficients of the regression lines did not differ significantly between the groups (7.7 (0.4) in group 15; 6.7 (0.3) in group 30; 7.5 (0.6) in group 60; and 7.7 (0.6) in group 90) and parallelism of the lines was demonstrated (Figure 1). Mean (SEM) ED_{50}, ED_{90} and ED_{95} obtained in group 15 (16.8 (0.5), 32.6 (1.7) and 40.9 (2.4) μg kg^{-1}, respectively) were significantly higher than those in other groups (10.6 (1.0), 20.8 (1.7) and 26.2 (2.2) μg kg^{-1}, respectively, in group 30; 11.2 (1.1), 21.7 (1.6) and 27.3 (1.8) μg kg^{-1}, respectively, in group 60; and 11.0 (1.1), 21.7 (1.6) and 27.5 (1.9) μg kg^{-1}, respectively, in group 90; $P<0.0001$) (Figure 1). There were no significant differences between the values obtained in groups 30, 60 and 90.

Discussion

Dose–response studies have frequently been used to estimate the potency of NMBAs and to compare them during anaesthesia.[1–3] It is recognized that the effect of a NMBA is altered by inhalational agents.[1–4] The mechanism of this potentiating effect is uncertain. However, this interaction seems to be a time-dependent phenomenon and to differ between inhalational agents.[5–8] Estimation and comparison of the potency of NMBAs should not be made unless the duration of exposure to an inhalational agent is constant. The required duration of exposure to an inhalational agent must also be determined before its maximum effect on neuromuscular block can be studied. It is important to take into consideration the relationship between the time course of potentiation and equilibration of anaesthetics to the neuromuscular compartment. Even though muscle tissue theoretically approaches equilibration with anaesthetic agents in 1–4 h,[11] the maximum effect of inhalational anaesthetics on NMBAs should occur more rapidly, as it has been demonstrated that the main potentiating effect of these agents on NMBAs is not direct inhibition of muscular contraction.[13] Potentiation of neuromuscular block is probably caused by depression of spinal motor neurones,[14] presynaptic inhibition of repetitive motor nerve firing[15] and acetylcholine release,[16] and decreased sensitivity of the postsynaptic acetylcholine receptor,[17] as well as an action on the muscle itself. Blood flow to the neuromuscular junction is far greater than that to muscle, so the time to reach equilibration and stabilization of the inhibitory effect

Table 1 Patient characteristics; mean (SD) values are given, there were no significant differences between groups

	Group 15	Group 30	Group 60	Group 90
Age (yr)	42.6 (28–56)	44.6 (25–58)	48.7 (30–57)	45.3 (28–58)
Gender (males/females)	4/6	3/7	4/6	4/6
Weight (kg)	56.2 (10.3)	56.8 (10.3)	57.8 (11.4)	52.4 (8.8)
Height (cm)	160.5 (10.5)	160.3 (9.0)	159.0 (8.8)	159.0 (7.9)

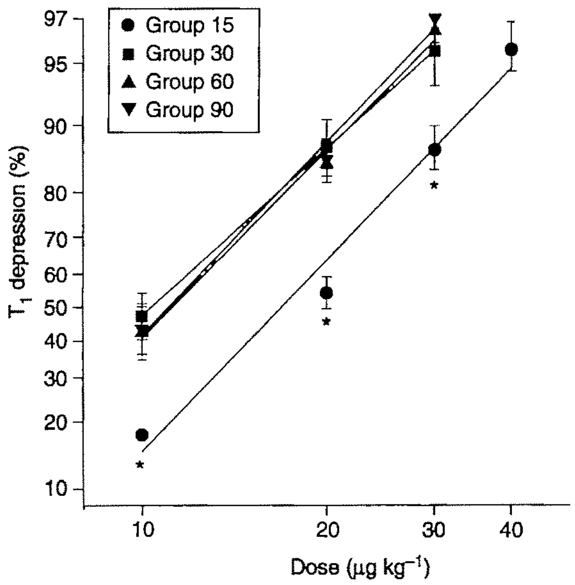

Fig 1 Mean cumulative dose–response relationships of vecuronium obtained in the four groups: group 15 (r^2=0.98), 30 (r^2=0.99), 60 (r^2=0.99) and 90 (r^2=0.99) The logit transformation of T_1 depression is plotted against the logarithm of the cumulative dose. Regression lines were constructed by least-squares regression analysis. Individual points represent mean ± SEM *Significantly different from the other groups (P<0.05).

of inhalational anaesthetics should be shorter at the neuromuscular junction than in muscle.

Sevoflurane has a low blood/gas and tissue/gas solubility,[10–12] so equilibration between the end-tidal concentration and the neuromuscular junction should be reached more rapidly with this agent than with other inhalational anaesthetics. We found a lower potency of vecuronium using dose–response studies after 15 min exposure to sevoflurane than after longer time periods. We suggest that the duration of sevoflurane anaesthesia influences the dose–response of vecuronium significantly and 30 min inhalation of an end-tidal concentration of 1.7% sevoflurane with nitrous oxide is sufficient to achieve a stable potentiating effect on vecuronium. The maximum potentiating effect of sevoflurane is therefore established more quickly than with other inhalational agents,[6 7] except for desflurane,[18] which is less soluble in blood and tissue than sevoflurane.[11 12] Meretoja and colleagues[6] showed that 1 MAC end-tidal concentration of halothane and isoflurane produced a maximal neuromuscular effect in ⩾30–80 min. Withington and colleagues[7] indicated that a longer exposure to 1 MAC end-tidal concentration of enflurane (45–120 min) was required to obtain a steady neuromuscular potentiating effect. In fact, the time course of augmentation by inhalational anaesthetics on NMBA differs markedly among the agents and sevoflurane seems to achieve the fastest onset of stable neuromuscular inhibition.

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Gram staining of protected pulmonary specimens in the early diagnosis of ventilator-associated pneumonia

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We evaluated prospectively the use of Gram staining of protected pulmonary specimens to allow the early diagnosis of ventilator-associated pneumonia (VAP), compared with the use of 60 bronchoscopic protected specimen brushes (PSB) and 126 blinded plugged telescopic catheters (PTC) obtained from 134 patients. Gram stains were from Cytospin slides; they were studied for the presence of microorganisms in 10 and 50 fields by two independent observers and classified according to their Gram stain morphology. Quantitative cultures were performed after serial dilution and plating on appropriate culture medium. A final diagnosis of VAP, based on a culture of $\geq 10^3$ c.f.u. ml^{-1}, was established after 81 (44%) samplings. When 10 fields were analysed, a strong relationship was found between the presence of bacteria on Gram staining and the final diagnosis of VAP (for PSB and PTC respectively: sensitivity 74 and 81%, specificity 94 and 100%, positive predictive value 91 and 100%, negative predictive value 82 and 88%). The correlation was less when we compared the morphology of microorganisms observed on Gram staining with those of bacteria obtained from quantitative cultures (for PSB and PTC respectively: sensitivity 54 and 69%, specificity 86 and 89%, positive predictive value 72 and 78%, negative predictive value 74 and 84%). Increasing the number of fields read to 50 was associated with a slight decrease in specificity and positive predictive value of Gram staining, but with a small increase in its sensitivity and negative predictive value. The results obtained by the two observers were similar to each other for both numbers of fields analysed. Gram staining of protected pulmonary specimens performed on 10 fields predicted the presence of VAP and partially identified (using Gram stain morphology) the microorganisms growing at significant concentrations, and could help in the early choice of the treatment of VAP. Increasing the number of fields read or having the Gram stain analysed by two independent individuals did not improve the results.

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Ventilator-associated pneumonia (VAP) is a serious complication in mechanical ventilation.[1] Inaccurate or delayed antibiotic therapy can affect the prognosis.[1 2] The best method of diagnosis for VAP is not clear. Protected specimen brushing (PSB) is a method with sensitivity of 90% and specificity of 75% if 10^3 colony-forming units (c.f.u.) ml^{-1} is taken as the threshold.[3] Blinded plugged telescopic catheter (PTC) sampling may also be reliable with the same threshold, although it seems more sensitive and less specific than PSB.[1 3] Whatever the method of sampling, a 24-h delay is needed for quantitative cultures, which limits early diagnosis. Gram staining of these protected pulmonary specimens could overcome this problem, but its diagnostic yield remains controversial.[1 3]

The present study was undertaken to evaluate prospectively whether the Gram stain of PSB or PTC predicts the results of quantitative cultures and can guide the choice the treatment of pneumonia. We also studied the possible improvement of the accuracy of Gram staining by analysing more fields or by having two independent observers analyse the stains.

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Patients and methods

Study population

We studied 134 successive adult patients in the medical and surgical intensive care units of the University Hospital of Bicêtre who were suspected of having nosocomial pneumonia. All had new and persistent pulmonary infiltrates on chest radiography that were unrelated to cardiogenic causes, macroscopically purulent tracheal aspirates, and leucocytosis (>12 000 cells mm^{-3}), and had been mechanically ventilated for at least 48 h. Although most (>90%) of the patients were febrile (>38.5°C), fever was not systematically used as a clinical criterion of pneumonia as some patients were given muscle relaxants.

One hundred and eight protected pulmonary specimens were taken from patients who had not received antimicrobial therapy during the previous 3 days, and 78 protected pulmonary specimens were taken from patients who had received antibiotics (for more than 72 h). No patient received local antimicrobial therapy or digestive decontamination with antibiotics.

Specimen collection

We obtained 126 PTC and 60 PSB samples after careful endotracheal suctioning and without topical anaesthesia.[3] The choice of one of these two techniques was left to the physician in charge of the patient. During the procedures, 100% oxygen was given and the patients were sedated with midazolam; pancuronium was used to achieve neuromuscular block. Heart rate, arterial pressure and arterial oxygen saturation were monitored during the investigation.

Blinded PTC samplings were performed by the previously described standardized technique.[4] The PTC unit was composed of an outer catheter sealed by a polyethylene glycol plug and an inner catheter for sampling. After blind introduction of a PTC unit into the bronchial system, the inner catheter was advanced, extruding the plug, and three brief aspirations were then applied to the inner catheter with a 10-ml syringe connected to its proximal port. After the catheter had been retracted into the outer sheath, the entire unit was removed from the patient; the distal end of the outer catheter was dried and then cut off with sterile scissors, the inner catheter was advanced, and 1 ml of saline was flushed through its proximal port and collected into a sterile vial. Finally, the distal segment of the catheter was transected and collected into the same vial. For the PSB, a bronchoscope (Olympus BF P 20D; Olympus Optical Corporation of America, New Hyde Park, NY, USA) was introduced through an adapter (Bodai Suction Safe Y; Sontek Medical, Lexington, MA, USA) and advanced to the bronchial orifice, selected according to the radiographic position of the new pulmonary infiltrate. After brushing, the tip of the PSB was cut aseptically and dropped into a sterile glass vial containing 1 ml of saline, according to a standard technique.[3] All the specimens were taken to the laboratory within 15 min of collection.

Microbiological processing

Microscopic examination

From the original suspension, 0.2-ml aliquots were dropped into a Cytospin and centrifuged at 300 *g* for 10 min. The slides were Gram-stained and independently examined twice (by A.K. and S.L.) at high magnification (×100) without knowledge of the quantitative culture results. The presence of microorganisms was looked for on 10 and 50 fields and any microorganisms found were classified according to their Gram stain morphology.

Quantitative cultures

Each vial was mechanically vortexed for 60 s. Two successive 1:100 saline dilutions were prepared. Aliquots (0.1 ml) of the original suspension and of each dilution were plated onto different media for quantitative culture and identification: fresh blood agar, fresh blood agar to which nalidixic acid, amphotericin B and colistin had been added, Drigalski agar, chocolate agar and anaerobic blood agar (BioMérieux, La Balme-les-Grottes, France). All samples were incubated for 48 h in an appropriate atmosphere and the microorganisms recovered were identified by standard methods and their number expressed as c.f.u ml^{-1}. The cut-off value of protected pulmonary specimens for the diagnosis VAP was $\geqslant 10^3$ c.f.u. ml^{-1}.[1]

Statistical analysis

Data are expressed as medians and ranges. To assess the degree of qualitative correlation between Gram staining and quantitative cultures, the results of Gram staining were divided into four categories. Gram staining was considered to be true-positive if each Gram stain morphotype present also grew at significant concentration (i.e. $\geqslant 10^3$ c.f.u. ml^{-1}), true-negative if no organism was present on Gram staining and quantitative culture was either sterile or non-significantly positive (i.e. $<10^3$ c.f.u. ml^{-1}), false-positive if a morphotype present on Gram staining was not grown in significant concentration, and false-negative if a microorganism grew at significant concentration but was not present on Gram staining. For mixed cultures, all the bacterial isolates grown at significant concentration had to be morphologically present on Gram staining. If not, the case was classified as false-negative. Similarly, the case was classified as false-positive if all the morphotypes present on Gram staining did not grow at significant concentration. Sensitivity, specificity and predictive value were calculated.[5] The Spearman rank test was used to assess the relationship between the number of bacilli and/or cocci seen on Gram staining and the number of microorganisms subsequently growing on appropriate culture medium;

Table 1 Performance of Gram staining in predicting ventilator-associated pneumonia when 10 fields were analysed by two independent observers. Values in parentheses are 95% confidence intervals

	Protected specimen brush (*n*=60)		Plugged telescopic catheter (*n*=126)	
	Observer 1	Observer 2	Observer 1	Observer 2
Sensitivity	74 (63–85)	74 (63–85)	81 (75–88)	72 (64–80)
Specificity	94 (88–100)	97 (93–100)	100 (95–100)	99 (97–100)
Positive predictive value	91 (84–98)	95 (89–100)	100 (95–100)	98 (96–100)
Negative predictive value	82 (72–92)	82 (72–92)	88 (83–93)	83 (76–90)

Table 2 Performance of Gram staining in predicting ventilator-associated pneumonia when 50 fields were analysed by two independent observers. Values in parentheses are 95% confidence intervals

	Protected specimen brush (*n*=60)		Plugged telescopic catheter (*n*=126)	
	Observer 1	Observer 2	Observer 1	Observer 2
Sensitivity (%)	88 (80–96)	81 (71–91)	91 (86–96)	80 (74–86)
Specificity (%)	89 (81–97)	91 (84–98)	96 (93–99)	96 (93–99)
Positive predictive value (%)	85 (76–94)	88 (80–96)	94 (90–98)	94 (90–98)
Negative predictive value (%)	91 (84–98)	86 (77–95)	93 (89–97)	86 (80–92)

$P<0.05$ was considered to be statistically significant. The κ statistic was used to measure the agreement between the two observers.[6] A κ value of 0 indicates no agreement beyond chance, whereas a κ value of 1 indicates perfect agreement.

Results

We studied 99 men and 35 women aged 56 (16–95) yr who had been in hospital for 9 (3–233) days. They had a final stay in the intensive care unit (ICU) of 24 (4–356) days and ICU mortality of 24%. The primary reasons for ventilation were trauma (78 patients), postoperative respiratory failure (12 patients), exacerbation of chronic obstructive pulmonary disease (18 patients), severe sepsis (23 patients) and acute pancreatitis (three patients). No adverse event was observed during any procedure.

Eighty-one (44%) protected pulmonary specimens (54 PTC and 27 PSB) had a positive culture, including 17 specimens with two (11 PTC and six PSB) or three (one PSB) microorganisms with different Gram stain morphologies. Microorganisms isolated at significant concentration were 24 *Staphylococcus aureus*, 1 isolate of coagulase-negative staphylococci, 7 *Streptococcus* spp., 10 *Streptococcus pneumoniae*, 1 *Neisseria* spp., 9 *Escherichia coli*, 14 *Haemophilus influenzae*, 2 *Proteus* spp., 1 *Klebsiella* spp., 4 *Enterobacter* spp., 3 *Serratia* spp., 19 *Pseudomonas aeruginosa*, 1 *Acinetobacter* spp., 1 *Stenotrophomonas maltophilia*, 2 *Branhamella catarrhalis*, and 1 *Bacteroides* spp. Ten patients (12%) died rapidly and the remaining 71 recovered from their bacterial pneumonia while receiving appropriate antibiotic therapy for organisms cultured at a significant growth in protected pulmonary specimens. The causes of death were overwhelming sepsis (*n*=2), multiple organ failure of unknown origin (*n*=5), brain death (*n*=2) and refractory hypoxaemia (*n*=1). Two (6%) of the 31 patients with a non-significant positive protected pulmonary specimen developed bacterial pneumonia (defined as a protected pulmonary specimen culture significantly positive and a clinical outcome consistent with pneumonia while receiving appropriate antibiotic therapy) caused by the same organisms 4 and 5 days later. None of the patients with a sterile protected pulmonary specimen culture later developed bacterial pneumonia during the 5 days after their inclusion in the study.

When 10 fields were analysed, a strong relationship was found between the presence of bacteria on Gram staining and the final diagnosis of VAP (Table 1). The ability of PTC Gram staining to predict VAP seemed better than that of PSB Gram staining, although the difference was not significant. Increasing the number of fields read to 50 was associated with a slight decrease in specificity and in the positive predictive value of the Gram stain, but with a small increase in its sensitivity and negative predictive value (Table 2). Whatever the number of fields read, the agreement between the two observers was excellent (κ=0.88 and 0.82 for 10 and 50 fields respectively).

The ability of Gram staining to predict which microorganisms subsequently grew at significant concentration when 10 fields were read is shown in Table 3. Again, the performance of PTC Gram staining was not significantly better than that of PSB Gram staining. Increasing the number of fields observed to 50 gave a slight decrease in specificity and in the positive predictive value of the Gram stain and a small increase in its sensitivity and negative predictive value (Table 4). The agreement between the two observers was also excellent (κ=0.87 and 0.85 when 10 and 50 fields were studied respectively).

Table 3 Performance of Gram staining in predicting the morphology of bacteria growing at significant concentration when 10 fields were analysed by two independent observers Values in parentheses are 95% confidence intervals

	Protected specimen brush (n=60)		**Plugged telescopic catheter (n=126)**	
	Observer 1	**Observer 2**	**Observer 1**	**Observer 2**
Sensitivity (%)	54 (43–67)	50 (37–63)	69 (61–77)	64 (56–72)
Specificity (%)	86 (77–95)	89 (81–97)	89 (84–94)	91 (86–96)
Positive predictive value (%)	72 (61–83)	75 (64–86)	78 (71–85)	81 (74–88)
Negative predictive value (%)	74 (63–85)	73 (62–84)	84 (78–90)	81 (74–88)

Table 4 Performance of Gram staining in predicting the morphology of bacteria growing at significant concentration when 50 fields were analysed by two independent observers. Values in parentheses are 95% confidence intervals

	Protected specimen brush (n=60)		**Plugged telescopic catheter (n=126)**	
	Observer 1	**Observer 2**	**Observer 1**	**Observer 2**
Sensitivity (%)	70 (58–82)	65 (53–77)	86 (80–92)	71 (63–79)
Specificity (%)	78 (68–88)	81 (71–91)	76 (69–83)	81 (76–86)
Positive predictive value (%)	67 (57–77)	68 (56–80)	58 (49–67)	64 (56–72)
Negative predictive value (%)	81 (71–91)	79 (69–89)	93 (89–97)	85 (79–91)

Whatever the number of fields studied or whoever performed the Gram stain analysis, a strong correlation ($P<0.001$) was found between the number of bacilli and/or cocci observed on Gram staining and the number of bacteria obtained in quantitative cultures.

Discussion

The diagnosis of bacterial pneumonia in severely ill, mechanically ventilated patients is difficult.[7] Diagnostic strategies for pneumonia range from a clinical approach to the use of invasive sampling. None of these strategies is without problems. The clinical approach may be too sensitive, and patients may be treated for pneumonia when a non-pulmonary infection or a non-infectious pulmonary process is present. Invasive sampling obviates the need for broad-spectrum antibiotic coverage for all patients with suspected pneumonia, reduces the risk of emergence of resistant microorganisms in the ICU and reduces the cost of antibiotic treatment. However, these techniques are expensive and need a specialized laboratory and specific clinical skills. Moreover, these techniques may be inaccurate in patients receiving antibiotics at the time of testing and may not be sensitive enough to diagnose all cases of ventilator-associated pneumonia, especially early infections.[8] No study has formally shown that the outcome of patients with ventilator-associated pneumonia can be improved if invasive methods are used in place of clinical diagnosis.

When invasive sampling is used, bacterial growth in the specimens is quantified and the presence of pneumonia and the identity of the causative pathogen(s) are defined by the recovery of bacteria at a concentration above a predetermined threshold ($\geqslant 10^3$ c.f.u. ml^{-1}).[7] Results are delayed until the quantitative cultures are available, and initial therapy is therefore empirical. Previous studies found that Gram staining of protected specimens had low sensitivity, prompting several authors to use microscopic analysis of bronchoalveolar lavage material along with quantitative cultures of protected specimens.[9, 10] The use of two invasive techniques in combination increases the cost, carries an additional risk for the patient and increases the difficulty and the work-load of the laboratory.

The present study shows that Gram staining of protected pulmonary specimens correctly predicts the presence of VAP and may partially identify (using Gram stain morphology) the microorganisms subsequently growing at significant concentrations. Our results support previous studies in which Gram staining was performed on slides prepared directly from the brushes. Teague *et al.* used two brushes, one for Gram staining and the other for quantitative culture, and found a marked correlation between Gram staining and the presence of bacteria at a concentration of $\geqslant 10^3$ c.f.u. ml^{-1}.[11] Similar results were reported by Pollock *et al.* when the brush was smeared directly onto a glass slide before the brush was placed in the holding medium.[12] In contrast, early studies using Gram staining on centrifuged specimens reported low sensitivity for the method.[4, 9, 13] More recently, Marquette *et al.* reported 85% sensitivity and 94% specificity for cytocentrifuged Gram staining.[14] The authors said they obtained good results because they first screened for bacteria using May-Grünwald Giemsa-stained slides at high magnification before performing (if these stains were positive) Gram staining on slides to determine the precise morphology of the bacteria detected. We believe that our results may be accounted for by several factors: cytocentrifuged preparations were made with a high, calibrated volume for the initial dilution (200 μl, i.e. 20% of the total dilution volume), and *Acinetobacter* spp., which may be detected either as Gram-negative coccobacilli or as Gram-positive cocci depending on its state of development, were rarely isolated. However, increasing the number of fields read or having the Gram staining analysed by two independent individuals were both time-consuming and did not usefully improve accuracy. Our results agree partially with those obtained previously when bronchoalveolar lavage was used to diagnose bacterial pneumonia. In a study reported recently in this journal, Gram staining of bronchoalveolar lavage was found to be useful for the rapid diagnosis of ventilator-associated pneumonia, but was not reliable for the early adaptation of empirical therapy.[15] By contrast, the role of Gram staining of tracheal aspirates was not useful in the diagnosis of ventilator-associated pneumonia or in guiding empirical therapy.[16]

Our study has several limitations. First, the effects on patient outcome and antibiotic management in relation to the data collected were not evaluated because Gram staining was generally performed many days after sampling and without knowledge of the results of quantitative cultures. Secondly, the performance of Gram staining of protected pulmonary specimens was not compared with results obtained by bronchoalveolar lavage or tracheal aspirates. However, it was not our policy to use such sampling methods routinely to investigate patients with suspected nosocomial pneumonia. The use of both invasive techniques in combination is expensive and time-consuming and carries an additional risk for the patient. Finally, PSB and PTC were considered as reference methods of diagnosing VAP. Until recently, lung histology has been considered the gold standard in this situation. However, when 39 open lung biopsies obtained from dead patients were reviewed independently by four pathologists, the prevalence of histological VAP, as determined by each of the pathologists, varied from 18 to 38%.[17] Histological features of VAP were found in seven of nine organ donors who had no clinical evidence of pulmonary infection and who were not receiving antibiotic therapy.[18] Finally, studies have found discrepancies between histology and bacteriological cultures. Neither the bacterial densities from the four quantitative airway cultures nor the bacterial density from the quantitative culture of lung parenchyma separated the histological pneumonia and non-pneumonia groups accurately.[19]

In summary, Gram staining of protected pulmonary specimens performed on 10 fields predicted the presence of VAP and partially identified (using Gram stain morphology) the microorganisms growing at significant concentrations. Further studies on antibiotic management and patient outcome, based on this method, are warranted.

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LABORATORY INVESTIGATIONS

Interaction of local anaesthetics with recombinant μ, κ, and δ-opioid receptors expressed in Chinese hamster ovary cells

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Local anaesthetics potentiate epidural or intrathecal opioid analgesia via a poorly defined mechanism. In this study, we have examined the interaction of local anaesthetics (lidocaine, bupivacaine and its optical isomers, tetracaine, procaine and prilocaine) with recombinant μ-, κ-, and δ-opioid receptors expressed in Chinese hamster ovary cells (CHO-μ, κ, and δ, respectively). Lidocaine produced a concentration-dependent displacement of radiolabelled opioid antagonist [^{3}H]diprenorphine ([^{3}H]DPN) binding with the following rank order of inhibitor constant (K_i): κ (210 μM) > μ (552 μM) > δ (1810 μM). Procaine, prilocaine, tetracaine and bupivacaine also displaced [^{3}H]DPN binding in CHO- μ with K_i values of 244, 204, 43 and 161 μM respectively. Lidocaine produced a concentration-dependent and naloxone-insensitive inhibition of cAMP formation in all cell lines including untransfected cells. Concentration producing 50% inhibition of maximum was μ, 1.32 mM; κ, 2.41 mM; δ, 1.27 mM; untransfected, 2.78 mM. When lidocaine (300 μM) was co-incubated with spiradoline (κ-selective) and [D-Ala^2, MePhe^4, Gly(ol)^5] enkephalin (DAMGO μ-selective) in CHO-κ and μ cells we did not observe an additive interaction for cAMP formation. In contrast, there was an apparent inhibitory action of the combination at the κ receptor. This study suggests that clinical concentrations of local anaesthetics interact with μ and κ but not δ opioid receptors. As there was no synergism between local anaesthetics and opioids we suggest that the interaction of these agents in the clinical setting does not occur at the cellular level.

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Clinically, local anaesthetics and opioids are commonly used in combination and are often administered into the epidural or intrathecal space in an attempt to manage postoperative pain and the pain of childbirth. These two classes of agents are reported to produce synergistic antinociceptive actions[1–7] such that addition of local anaesthetic can reduce the dose of opioid used and hence reduce the number and severity of any adverse reactions.

Local anaesthetic agents produce a use dependent block of voltage dependent Na$^+$ channels, and hence, reduce axonal conduction.[8] Opioid receptors are classified as μ, κ and δ and all have been cloned and expressed in a variety of cells and display pharmacology consistent with the receptors previously identified. Opioid receptor activation activates an inwardly rectifying K$^+$ channel (K_{ir}-hence promoting an efflux of K$^+$) and closes voltage sensitive Ca^{2+} channels resulting in membrane hyperpolarization, reduced Ca^{2+} influx, and hence, reduced neurotransmission. Adenylyl cyclase is also inhibited leading to reduced cAMP formation.[9–14] This reduced cAMP formation is often measured as a biochemical index of opioid receptor activation but may also be involved in reduced neuronal firing via an interaction with the inwardly rectifying K$^+$ channel (I_h).[15]

The mechanism and site(s) of opioid-local anaesthetic interaction are yet to be fully described. Several potential sites are possible. These include: changes in opioid pharmacokinetics (i.e. changes in tissue pH) produced by local anaesthetics;[5] potentiation of the inhibitory effect of opioids on neurotransmitter release via modulation of

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second messenger systems such as adenylyl cyclase;[12 14 16] or actions at voltage sensitive Ca^{2+} channels.[17 18] A direct interaction of local anaesthetics with opioid receptors has also been suggested.[7]

In this study, we have tested the latter hypothesis, that local anaesthetics interact with opioid receptors and that this may modulate the formation of cAMP. In order to avoid the interpretation problems associated with cell and tissue studies of a heterogeneous population of endogenous receptors, we have utilized Chinese hamster ovary (CHO) cells expressing recombinant μ-, κ-, and δ-opioid receptors (CHO-μ, κ, and δ, respectively).

Materials and methods

Sources of reagents

All tissue culture media and supplements were from Life Technologies (UK). With the exception of bupivacaine isomers all local anaesthetic agents were from Sigma (Poole, UK). S(−)bupivacaine (Batch OA859/15) and R(+)bupivacaine (Batch OA314/14) were from Astra Pain Control (Sweden). [^{3}H]Diprenorphine (DPN) (specific activity 41 Ci mmol^{-1}) was from Amersham International (Bucks, UK). [2,8–^{3}H]cAMP (28.4 Ci mmol^{-1}) was from NEN DuPont (Boston, MA). All other drugs were from Sigma (Poole, UK) or Calbiochem (Notts., UK). Other reagents were of the highest purity available.

Membrane preparation and cell culture

CHO-μ, κ, δ cells[19–21] and untransfected CHO wild-type (CHO-wt) cells (i.e. cells not expressing the plasmid that encodes the receptor of interest and, therefore, acting as negative controls) were grown for experimentation in Hams F12 medium supplemented with penicillin 100 iu ml^{-1}, streptomycin 100 μg ml^{-1}, fungizone 2.5 μg ml^{-1} and fetal calf serum 10%. (Stock cultures also contained G418 200 μg ml^{-1}.) Cultures were maintained at 37°C in 5% CO_2/ humidified air at 37°C, fed every 2–3 days and passaged every 7 days. Experiments were performed at days 5–7 after subculture. All cells were harvested for use by the addition of saline 0.9% containing HEPES (10 mM)/EDTA (0.02%). Cells were homogenized at 4°C using a tissue Tearor (setting 5.5×30-s bursts) in 50 mM Tris–HCl buffer (pH 7.4). The homogenate was centrifuged at 18 000 ×g for 10 min and the pellet resuspended in Tris–HCl buffer. This procedure was repeated twice more. Membranes were prepared and used fresh daily.

[^{3}H]DPN binding

The binding of the non-selective opioid receptor antagonist [^{3}H]DPN was performed in 1 ml volumes of Tris–HCl buffer containing approximately 200 μg of membranes at 20°C for 90 min as described previously.[22] Non-specific binding was defined in the presence of naloxone 10 μM. Following incubation, each sample was filtered (and washed) under vacuum through Whatman GF/B filters using a Brandel cell harvester. Filter retained radioactivity was extracted for at least 8 h in 4 ml of scintillation fluid. In displacement studies, the interaction of lidocaine (10^{-6} to 10^{-2} M) with μ, κ and δ-opioid receptors, and of bupivacaine (10^{-6} to 3×10^{-3} M) and its enantiomers (S(−) and R(+): 10^{-6} to 10^{-2} M), procaine (10^{-6} to $\times10^{-2}$ M), prilocaine (10^{-6} to 3×10^{-2} M), and tetracaine (10^{-6} to 10^{-2} M) with μ-opioid receptor were determined by displacement of ~0.5 nM [^{3}H]DPN.

Measurement of cAMP formation

Whole cells (CHO-μ, κ, δ and wt) suspended in 0.3 ml Krebs–HEPES buffer, pH 7.4 were incubated in the presence of isobutylmethylxanthine (1 mM) with or without (for the basal) forskolin (10 μM) at 37°C for 15 min. To obtain a concentration response curve for lidocaine inhibition of cAMP formation, cells were incubated additionally with or without lidocaine (10^{-5} to 3×10^{-2} M). In order to determine any naloxone-sensitivity of lidocaine inhibition of cAMP formation, CHO-μ, κ or δ cells were incubated with lidocaine 2 mM in the presence or absence of naloxone 10 μM. In addition some cells were co-incubated with lidocaine (300 μM) and subtype selective opioid agonists: (D-Ala^2, MePhe^4, Gly(ol)^5) enkephalin (DAMGO: 100 nM) for μ and spiradoline (2 nM) for κ. Reactions were terminated by the addition of 20 μl HCl (10 M), 20 μl NaOH (10 M) and 180 μl Tris buffer (1 M, pH 7.4). The concentration of cAMP was measured in the supernatant following centrifugation (13 000 r.p.m./2 min) using a specific protein binding assay as described previously.[22]

Statistical analysis

All data are expressed as mean (SEM). The log concentration of displacers producing 50% displacement of specific binding (IC_{50}) and the concentration of local anaesthetic producing 50% maximum inhibition of forskolin stimulated cAMP formation (IC_{50}) were obtained by computer assisted curve fitting (GRAPHPAD-PRISM). IC_{50} values from binding experiments were additionally corrected for the competing mass of [^{3}H]DPN according to Cheng and Prusoff[23] to yield the inhibitor constant (K_i). Further terminology follows IUPHAR recommendations where B_{max} is defined as the maximum specific binding of a ligand determined in a radioligand binding assay (an estimate of the number of receptors), and K_d is the equilibrium dissociation constant (calculated as ligand concentration at 0.5 B_{max}). Additivity data are analysed using an unpaired t-test with $P<0.05$ considered to represent a significant difference.

Results

[^{3}H]DPN binding

Saturation analyses performed previously with these cells yielded B_{max} and K_d values of (mean (SEM)) 262 (3), 70 (2), 279 (4) fmol mg protein^{-1} and 85 (5), 91 (6), 372 (15) pM in CHO-μ, κ, and δ respectively.[24] In displacement studies, lidocaine produced a concentration-dependent displacement of [^{3}H]DPN binding to all opioid receptor subtypes (Fig. 1A) with the following rank order potency (mean K_i in μM): κ (210) > μ (552) > δ (1810). A range of other local anaesthetics also displaced [^{3}H]DPN binding to μ receptors (Fig. 1B) with K_i values shown in Table 1. Whilst it was not possible to produce full displacement curves for R(+) bupivacaine and S(−) bupivacaine with the quantity available to us there was a suggestion of some stereoselectivity (R(+) more potent than S(−)) in CHO-μ and κ but not δ (Fig. 2).

Inhibition of forskolin-stimulated cAMP formation

Lidocaine produced a concentration-dependent (Fig. 3A) but naloxone-insensitive (Fig. 3B) inhibition of forskolin stimulated cAMP formation in all cell lines including untransfected CHO-wt cells. The IC_{50} values were not significantly different among the cell lines examined (Table 2). The interaction of lidocaine with the κ and μ receptor occurred at clinically achievable concentrations and was probed further. As our initial premise was to determine if there was an interaction between opioids and local anaesthetics, we examined the effects of lidocaine in the presence of the selective κ and μ agonists spiradoline (2 nM) and (D-Ala^2, MePhe^4, Gly(ol)^5) enkephalin (DAMGO, 100 nM); these concentrations were chosen from a previous study[24] and were close to their IC_{50} for inhibition of cAMP formation. Lidocaine at 300 μM was chosen as this produced a significant displacement (50–70%, Fig. 1) of the binding of [^{3}H]DPN but only a small inhibition (<20%, Fig. 3) of cAMP formation. Both spiradoline and DAMGO inhibited forskolin stimulated cAMP formation in CHO-κ and μ cells respectively. This was naloxone (10 μM) sensitive (data not shown). The measured combination of lidocaine and spiradoline was significantly lower than the value predicted. A similar trend was observed for the lidocaine–DAMGO combination but this failed to reach statistical significance (Table 3). Due to the direct inhibitory action of lidocaine on cAMP formation it was not possible to probe this effect further.

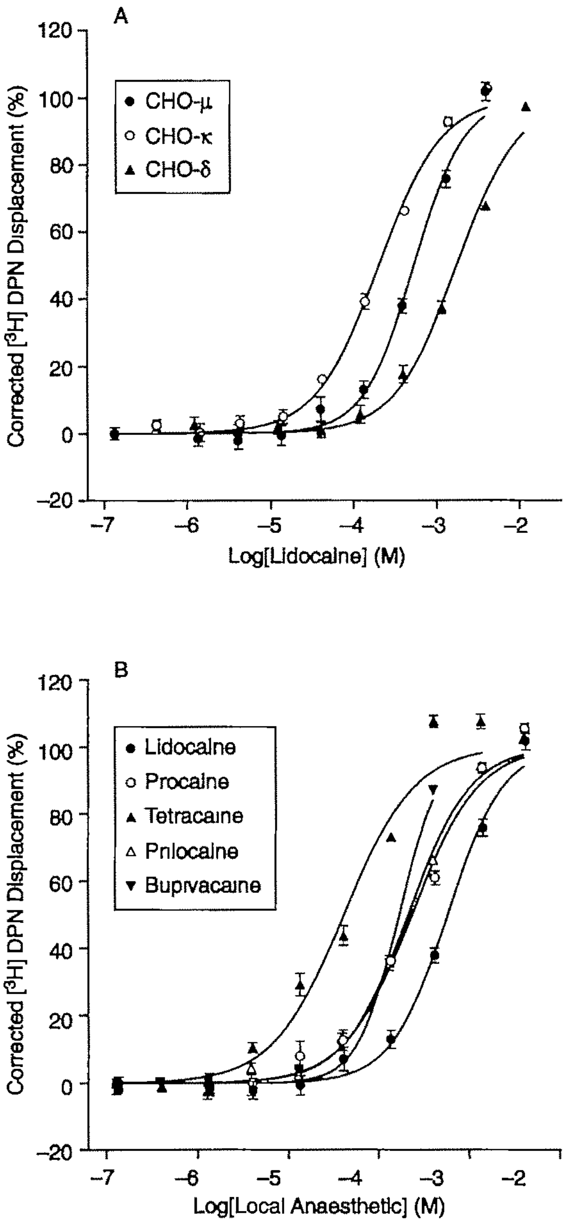

Fig 1 (A) Lidocaine concentration-dependently displaced [^{3}H]DPN from CHO-κ, μ and δ with the following rank order: κ > μ > δ. (B) Interaction of a range of local anaesthetics with μ-opioid receptor. Concentration–response curves are corrected for the competing mass of [^{3}H]DPN according to Cheng and Prusoff.[23] All data are mean (SEM) (n=5).

Discussion

In this study we have shown a clear interaction of a range of local anaesthetic agents encompassing both ester and amide forms with recombinant opioid receptors. Few studies examine *both* receptor and post-receptor events. For lidocaine there appeared to be some subtype selectivity; κ (210 μM) > μ (552 μM) > δ (1810 μM). In general, the calculated local anaesthetic K_i for [^{3}H]DPN displacement from μ-opioid receptors (and lidocaine in CHO-κ cells) fell within the clinical concentration range encountered during spinal anaesthesia,[17 25 26] although we could not find similar

Table 1 K_i values (this study mean (95% CI)) for local anaesthetic binding to the μ receptor in this study and for other G-protein coupled receptors (β_2-adrenoceptor, β_2AR, Histamine, H_1, muscarinic, mACh) compared with relative (to procaine=1) C-fibre conduction block. Local anaesthetic agents are ranked according to their hydrophobicity [a] [^{3}H]DHP binding.[29] [b] [^{3}H]mepyramine binding.[30] [c] [^{3}H]QNB binding.[31] [d] From Strichartz and Berde.[8] ND, not determined

Local anaesthetic	**K_i mM (95%CI) this study**	**K_i β_2AR[a]**	**pK_i H_1[b]**	**mACh[c] pK_i**	**Rel. cond. block[d]**
Tetracaine	42 8 (35 8–51.7)	2.5	52 5	109 6	8 0
Bupivacaine	161 3 (147.2–177.0)	79.4	ND	9772	8 0
Lidocaine	552 1 (427.6–712 9)	251.2	ND	3715	2 0
Prilocaine	203 7 (184 1–225 4)	158.5	ND	1585	3 0
Procaine	243 8 (178 6–332 7)	63 1	107.2	870 9	1 0

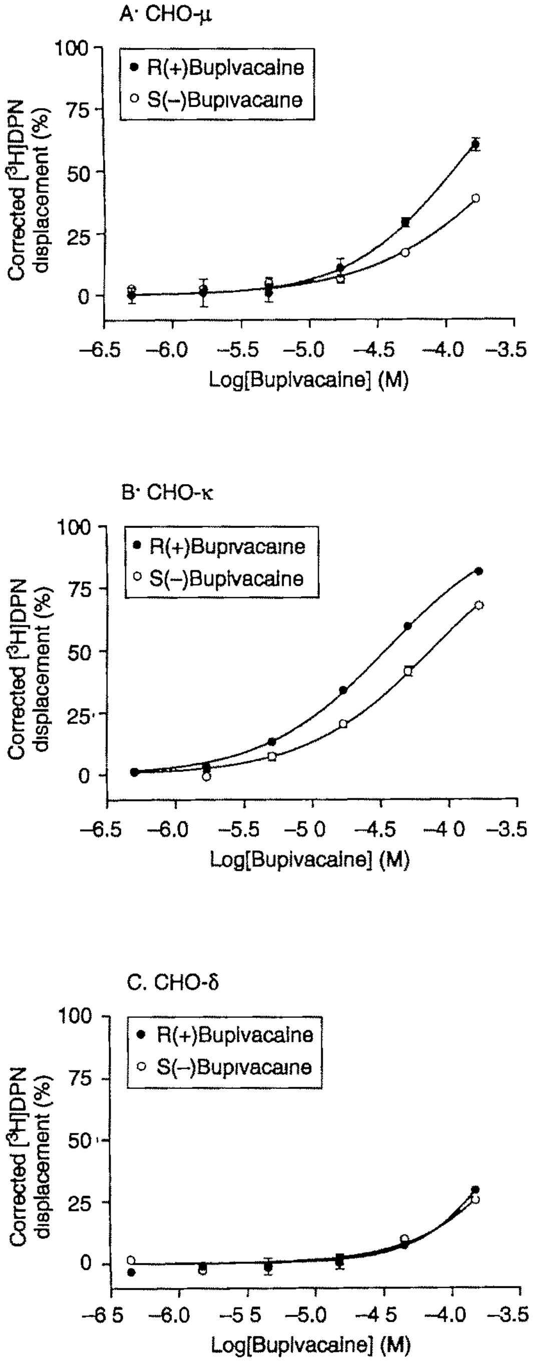

Fig 2 Interaction of bupivacaine isomers with μ- (A), κ- (B) and δ (C)-opioid receptors. All data are mean (SEM) (n=5). For CHO-μ and -κ, there is a suggestion of stereoselectivity (i.e. the curve for S(−)bupivacaine tends to the right)

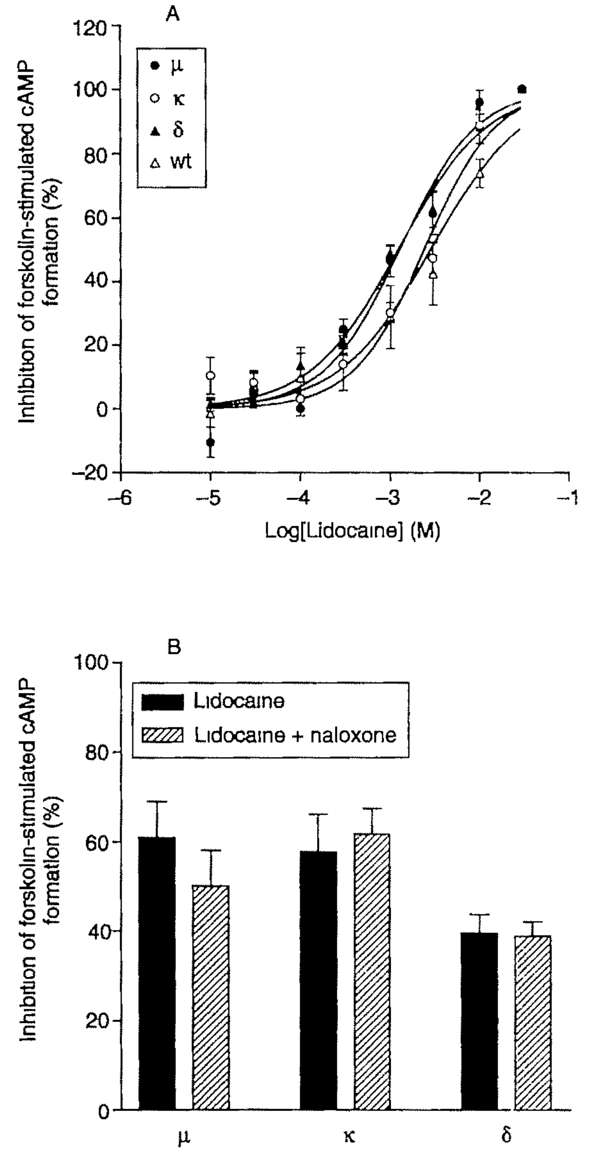

Fig 3 (A) Lidocaine produced a concentration-dependent inhibition of forskolin-stimulated cAMP formation in CHO cells expressing μ, κ, δ opioid receptors (CHO-μ, κ, δ) and in untransfected wt cells (B) Lidocaine-induced inhibition of forskolin-stimulated cAMP formation was naloxone insensitive. All data are mean (SEM) (n=4–5)

concentrations for procaine and prilocaine. However, we were unable to conclusively define the functional consequences of this interaction.

Table 2 IC_{50} (mM) for inhibition of cAMP formation by lidocaine CHO-wt, untransfected CHO wild type cells. Mean (95%CI) from n=4

	CHO-μ	**CHO-κ**	**CHO-δ**	**CHO-wt**
IC_{50}	1.32 (0.73–2.38)	2 41 (1.50–3.90)	1.27 (0 71–2 28)	2.78 (1 63–4 73)

Table 3 Interaction of lidocaine (300 μM) with spiradoline (2 nM) and (D-Ala^2, MePhe^4, Gly(ol)^5) enkephalin (DAMGO, 100 nM) in CHO-κ and μ cells respectively. % inhibition of forskolin stimulated cAMP formation are presented as mean (SEM) (n=4–11). ^{a}$P<0.05$ significantly inhibited compared to paired forskolin (paired Student's t-test), ^{b}$P<0$ 05 significantly greater than lidocaine alone (unpaired Student' t-test), ^{c}$P<0$ 05 significantly reduced compared with predicted lidocaine+spiradoline (unpaired Student's t-test)

Combination	**% Inhibition of cAMP formation**
CHO-κ	
Lidocaine	9 6 (1.6)^a
Spiradoline	18.0 (2.3)^{ab}
Lidocaine + spiradoline (predicted if additive)	27.6 (4 1)^{ab}
Lidocaine + spiradoline (measured)	14 9 (2.8)^{ac}
CHO-μ	
Lidocaine	17 4 (6.8)^a
DAMGO	24 7 (2.8)^a
Lidocaine + DAMGO (predicted if additive)	42 1 (10.6)^a
Lidocaine + DAMGO (measured)	25.6 (3 9)^a

Local anaesthetic agents have been shown to interact with a number of differing receptor systems including ligand gated ion channels and G-protein coupled receptors. For example, the GABA$_A$ receptor[27] and nicotinic receptor[28] are ligand gated ion channel coupled receptors whose activity is inhibited by local·anaesthetics. Interestingly, in the latter study, glutamate, NMDA and AMPA receptors were unaffected.[28] Some examples of the interaction of local anaesthetic agents with G-protein coupled receptors are shown in Table 1.[29–31] For this receptor system there does not appear to be any significant correlation with relative conduction blocking potency but the rank order potency at the μ opioid receptor follows the hydrophobicity ranking.

A possible target for the interaction of local anaesthetics and opioids is the opioid receptor and the elements of the signal transduction cascade associated with this receptor, i.e. adenylyl cyclase, voltage sensitive Ca^{2+} channels and inwardly rectifying K$^+$ channels. Tejwani and colleagues[7] reported that bupivacaine inhibited the specific binding of a range of radioligands to μ-receptors but surprisingly increased binding to κ- and δ-receptors. However, in a radioligand binding study, Fraser and Fowler[32] reported that local anaesthetics did not interact with κ-opioid receptors. The discrepancy between these and our study most likely results from the concentration of local anaesthetic used. In the studies of Tejwani and colleagues[7] and Fraser and Fowler[32] bupivacaine concentration of less than 10 μM were used. The present data indicates that significant inhibition of radioligand binding to opioid receptors requires bupivacaine concentrations in excess of 10 μM (K_i, 161 μM).

In a review article, Franks and Lieb[33] suggested that stereoselectivity may prove to be one of the most powerful guides to *in vitro* targets relevant to anaesthesia. In the present study (with the amount of bupivacaine isomers available to us) our data give an indication of some stereoselectivity for bupivacaine at μ- and κ- but probably not δ-opioid receptors (Fig. 3) with the R(+) isomer being more potent than the S(–) isomer. However, this stereoselectivity is the reverse of that observed for neuronal Na$^+$ channels (S(–) more potent than (R(+))[34] and we have no explanation for this discrepancy. Despite the conclusions of Fraser and Fowler[32] to the contrary, our data suggest that the μ- and κ-opioid receptors may represent a target for local anaesthetic agents and a site at which the clinically observed local-opioid interaction may occur. In this study, we probed the functional consequences of this interaction further by studying the effects of opioids and lidocaine on the formation of cAMP.

Opioid receptor agonists inhibit adenylyl cyclase thus inhibiting cAMP formation through opioid receptors and this may give clues as to an interaction with G_i coupled voltage sensitive Ca^{2+} channels and K_{ir}. In addition, Wang and colleagues[35] reported that cAMP mediated μ and δ but not κ opioid analgesia, based on the reversal of μ and δ-mediated analgesia by intrathecal administration of dibutyl-cAMP (i.e. artificially elevating cAMP). In the present study lidocaine inhibited forskolin-stimulated cAMP formation in a concentration-dependent and naloxone insensitive manner indicating that this inhibitory action on adenylyl cyclase was not mediated via opioid receptors. This was further confirmed in untransfected CHO cells where lidocaine also inhibited cAMP formation with an essentially identical pIC_{50} when compared with CHO-κ, μ and δ cells. These data are also consistent with the observed direct interaction of local anaesthetics with the catalytic subunit of adenylyl cyclase leading to reduced cAMP formation.[16] Thus, whilst the formation of cAMP is, as would be expected for opioids, inhibited by lidocaine, this response does not represent agonist action at the opioid receptor. If local anaesthetic agents and opioid receptor activation inhibit cAMP formation by different pathways then it might be reasonable to assume that the combination of local and opioid would produce an additive inhibition. This was clearly not the case (Table 3). Indeed we have found a suggestion of an inhibitory action of lidocaine on κ (and possibly μ) receptor signaling. We cannot explain the lack of a positive interaction between these two agents at the level of cAMP formation.

Our data suggest that the interaction between local anaesthetic agents and opioids in the clinical setting does not result from an interaction with opioid receptor signaling (i.e. at the cellular level). It is well known that opioids inhibit cAMP formation, close voltage sensitive Ca^{2+} channels and activate inwardly rectifying K^{+} channels. These combined actions are likely to reduce neurotransmission. It is also well known that local anaesthetic agents inhibit voltage sensitive Na^{+} channels to reduce axonal conduction. Na^{+} channel blockade with local anaesthetics produces analgesia. It is worthy of mention that a range of anticonvulsants with analgesic activity also appear to inhibit voltage sensitive Na^{+} channels. For example, carbamazepine[36] and gabapentin[37] block Na^{+} channels and are also useful in the pain clinic. The actions of lamotrigine are equivocal where Na^{+} channel block[36] and facilitation of C-fibre responses[38] have also been reported.

We therefore conclude that the clinical interaction between local anaesthetic agents and opioids may occur as a combination of reduced axonal conduction and neurotransmission in the spinal cord and an interaction at the cellular level is unlikely.

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Intrathecal cyclooxygenase inhibitor administration attenuates morphine antinociceptive tolerance in rats

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Several lines of evidence suggest that the *N*-methyl-D-aspartate receptor (NMDA) and nitric oxide (NO) systems are involved in morphine tolerance. Cyclooxygenase (COX) inhibitors may also play a role in morphine tolerance by interacting with both systems. In the present study, we examined the effects of the COX inhibitors *N*-(2-cyclohexyloxy-4-nitrophenyl) methanesulphonamide (NS-398, selective COX_2 inhibitor) and indomethacin (non-selective COX inhibitor) on the development of antinociceptive tolerance of morphine in a rat spinal model. The antinociceptive effect was determined by the tail-flick test. Tolerance was induced by injection of morphine 50 μg intrathecally (i.t.) twice daily for 5 days. The effects of NS-398 and indomethacin on morphine antinociceptive tolerance were examined after administering these drugs i.t. 10 min before each morphine injection. Neither NS-398 nor indomethacin alone produced an antinociception effect at doses up to 40 μg. NS-398 and indomethacin did not enhance the antinociceptive effect of morphine in naïve and morphine-tolerant rats. However, they shifted the morphine antinociceptive dose–response curve to the left when co-administered with morphine during tolerance induction, and reduced the increase in the ED_{50} of morphine (dose producing 50% of the maximum response) three- to four-fold. Collectively, these findings and previous studies suggest that COX may be involved in the development of morphine tolerance without directly enhancing its antinociceptive effect.

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Non-steroidal anti-inflammatory drugs (NSAIDs) produce their therapeutic effect by inhibiting COX activity, thus reducing the synthesis of prostaglandins (PGs).[1] Combinations of NSAIDs with morphine have been used in clinical pain management, particularly in terminal cancer patients.[2] The potential advantages of this combination are that analgesia can be maximized while minimizing the adverse effects of morphine. Animal and clinical studies have shown additive or, possibly, synergistic interaction between opioids and NSAIDs.[3 4] Interactions between NSAIDs and morphine have also been reported in the visceral nociception and neuropathic pain models.[5 6]

There is a large body of evidence indicating the involvement of the NMDA receptor and NO systems in opioid tolerance. NMDA antagonists and NO inhibitors have been shown to attenuate or prevent morphine tolerance.[7–14] Recently, we further demonstrated that NMDA receptor antagonists inhibit morphine tolerance not only by modulating the binding characteristics of μ-opioid receptors[11] but also by partially preventing the constitutive neuronal expression of NO synthase (NOS).[14]

Mao *et al.* proposed that opioid tolerance and neuropathic pain syndromes share a common intracellular mechanism; both are expressed as a loss of analgesic effect of opioids.[15] In addition, Malmberg and Yaksh reported that NSAIDs could attenuate the hyperalgesia mediated by glutamate receptors.[16] Interaction between NMDA- and PG receptor-mediated events during inflammatory nociception has also been reported.[17] PGE_2 was shown to stimulate the release of NO from rat spinal cord by NMDA receptor activation through EP1 receptors.[18] Moreover, cross-communication between the NOS and COX systems has also been

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demonstrated.[19 20] NO interacts directly with COX to enhance its enzymatic activity.[19] Inducible NOS activation may increase NO release and subsequently increase PG release, via COX activation.[20] These findings imply complicated interactions among NMDA receptors and the NO and COX systems. In the light of these findings, we propose that COX inhibitors modulate antinociceptive tolerance of morphine via interaction with the NMDA–NO system. The present study was designed to examine the effects of the COX-selective inhibitors NS-398 (a selective COX_2 inhibitor) and the non-selective COX inhibitor indomethacin on the development of morphine antinociceptive tolerance in a rat spinal model.

Materials and methods

The experimental protocol was approved by the Animal Care and Use Committee of the National Defense Medical Center. Male Sprague–Dawley rats (weighing 300–350 g) were anaesthetized with intraperitoneal chloral hydrate (400 mg kg^{-1}), and intrathecal (i.t.) catheters were implanted for drug administration. The rats were then housed in the animal facility at the National Defense Medical Center for a 3-day recovery period. The antinociceptive effects of various drugs were measured by the tail-flick test, as in our previous studies.[11 14] A microsyringe (Hamilton, 25 µl) was attached to the i.t. catheter (PE_{10}) for drug administration. Drugs were administered in 5 µl of solution, and drug administration was followed by flushing with 10 µl of saline. Morphine sulphate was purchased from the Narcotics Control Bureau of the Health Department of the Republic of China (Taiwan), and was dissolved in saline. The antinociceptive effects of NS-398 and indomethacin were examined, and the effects of i.t. administration of NS-398 and indomethacin on morphine antinociceptive tolerance were examined by injecting these drugs 10 min before morphine administration. Antinociceptive responses were examined 30 min after morphine injection. The thermal intensity used in the tail-flick test was determined from the mean tail-flick latency (3.0±0.1 s) of 30 rats injected with saline before the study.

In a preliminary study, the effect of 30 µg of NS-398 or indomethacin, alone or with morphine, was not significantly different from that of of 20 µg in the tail-flick test. Therefore, a dose of 20 µg (i.t.) was used for NS-398 and indomethacin in the present study. Tolerance to the antinociceptive effect of morphine was induced by injection of morphine (50 µg, i.t.) twice daily for 5 days. To investigate the effects of COX inhibitors (NS-398 and indomethacin, 20 µg) on morphine tolerance, we calculated the ED_{50} for morphine antinociception after morphine tolerance had developed. The COX inhibitors were administered 10 min before each morphine injection on each of the 5 days of tolerance induction. The effects of COX inhibitors on the morphine antinociceptive dose–response curve were examined on the first and fifth days of tolerance induction. The tail-flick test was performed daily.

The tail-flick response was converted from a defined latency to the maximum per cent effect (MPE) as follows:

$$\mathrm{MPE\%} = \frac{(\text{maximum latency} - \text{baseline latency}) \times 100}{\text{cut-off latency}(10\,\text{s}) - \text{baseline latency}}$$

NS-398 and indomethacin (Cayman, MI, USA) were dissolved in dimethyl sulphoxide (DMSO) and saline (1:1). DMSO had no significant effects on antinociception using the tail-flick test.[21]

The morphine antinociceptive dose–response latency was analysed by computer-assisted linear regression (Cricket Graph 1.32; Islandia, NY, USA). The ED_{50} was defined as the morphine dose that induced a 50% MPE measured by the tail-flick test and was calculated using the linear regression equations. All data are presented as mean and SEM. The data were subjected to analysis of variance and the Dunnett test, and P values <0.05 were considered significant.

Results

Intrathecal administration of NS-398 or indomethacin alone failed to produce any antinociceptive effect (Fig. 1). The maximum antinociceptive effect of morphine was observed on day 1 during the induction of morphine tolerance (Fig. 2). The tail-flick latency for NS-398 or indomethacin co-administered with morphine was higher than that of morphine alone, but the difference was not statistically significant. Morphine antinociceptive tolerance developed by day 3. Morphine maintained an antinociceptive effect when co-administered with NS-398 or indomethacin during tolerance induction; i.e. both NS-398 and indomethacin attenuated morphine antinociceptive tolerance (P<0.01) (Fig. 2). On day 5, maximum tolerance was attained in the rats treated with morphine alone. Neither indomethacin nor NS-398 treatment alone produced any antinociceptive effect

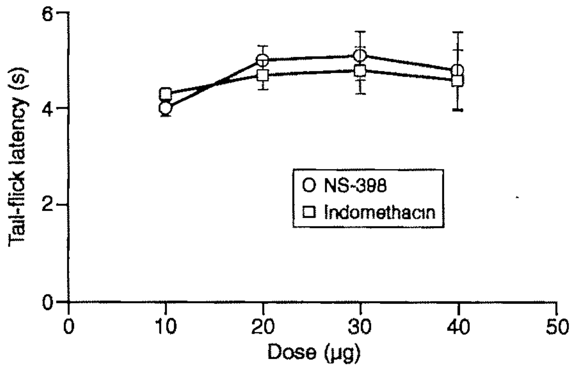

Fig 1 The thermal antinociceptive effects of intrathecally administered NS-398 and indomethacin in rats, determined by the tail-flick test Neither drug had any antinociceptive effect. All data points are mean and SEM for at least six rats.

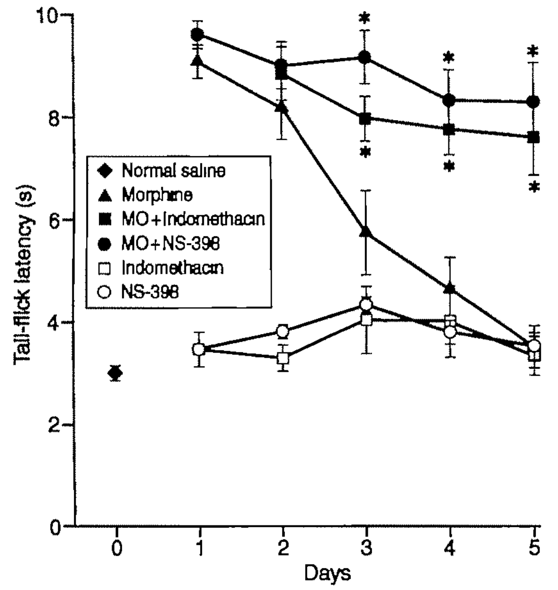

Fig 2 The effects of NS-398 and indomethacin on the development of morphine tolerance. Tolerance was induced by injection of morphine (50 μg, i.t.) twice daily for 5 days. Tail-flick latency was measured on each of these 5 days. The effects of NS-398 or indomethacin on the development of morphine tolerance were tested by administering NS-398 (20 μg, i.t.) or indomethacin (20 μg, i.t.) 10 min before each morphine injection during tolerance induction. The antinociceptive effects of NS-398 (20 μg, i.t.) and indomethacin (20 μg, i.t.) alone were also examined on each of the 5 days. The ◆ shows the mean tail-flick latency of 30 rats injected with saline before the study. All data points are mean and SEM for at least six rats $^*P<0.01$ compared with the group injected with morphine alone.

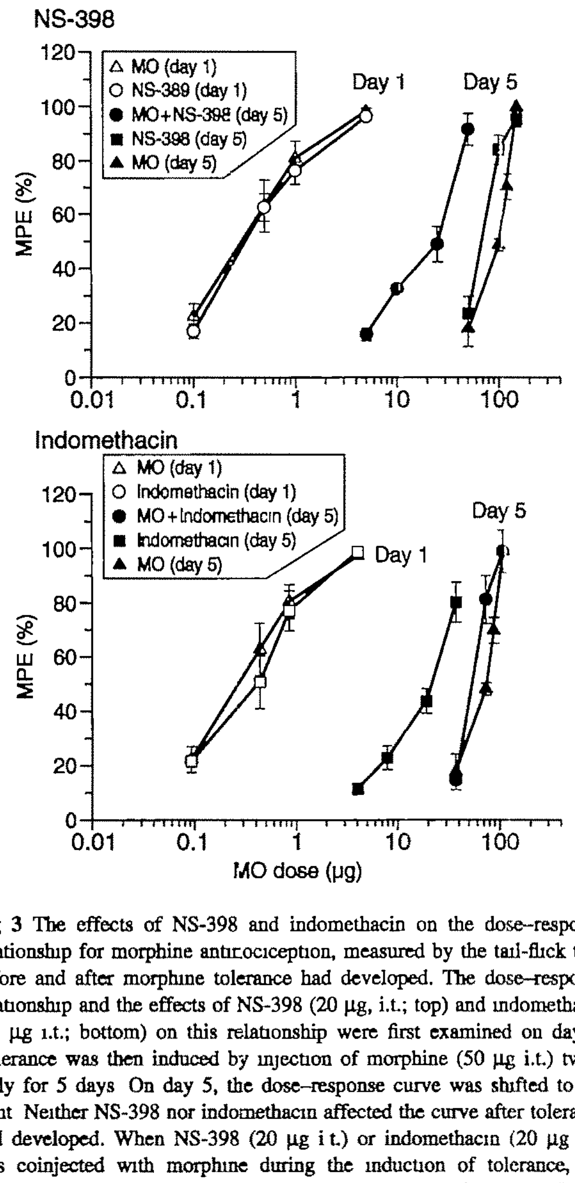

Fig 3 The effects of NS-398 and indomethacin on the dose–response relationship for morphine antinociception, measured by the tail-flick test, before and after morphine tolerance had developed. The dose–response relationship and the effects of NS-398 (20 μg, i.t.; top) and indomethacin (20 μg i.t.; bottom) on this relationship were first examined on day 1. Tolerance was then induced by injection of morphine (50 μg i.t.) twice daily for 5 days On day 5, the dose–response curve was shifted to the right Neither NS-398 nor indomethacin affected the curve after tolerance had developed. When NS-398 (20 μg i.t.) or indomethacin (20 μg i.t.) was coinjected with morphine during the induction of tolerance, the morphine dose–response curves were shifted to the left on day 5. All data points are the mean and SEM for at least six rats.

Table 1 Effects of NS-398 and indomethacin on the ED_{50} values for morphine antinociception after intrathecal injection of morphine twice daily for 5 days. The ED_{50} values were calculated from the antinociceptive dose–response curves shown in Fig. 3

	Day 1 (μg)	Day 5 (μg)	Increase in ED_{50} (fold)
Morphine	0.51	85.12	166.9
Morphine + NS-398	0.43	17.38	40.4
Morphine + indomethacin	0.42	22.19	53.3

during the 5-day test (Fig. 2). As in our previous study[14], normal saline injections did not influence tail-flick latency in the rats used as controls (data not shown).

The effects of COX inhibitors on the morphine antinociception dose–response curve in morphine-tolerant rats are shown in Fig. 3. On day 1, morphine administration (0.1–5 μg, i.t.) produced a dose-dependent antinociceptive effect, with an ED_{50} of 0.51 μg (Table 1). Co-administration of a COX inhibitor (NS-398 or indomethacin) did not change the morphine antinociception dose–response curves either before (day 1) or after (day 5) morphine tolerance had developed (Fig. 3). However, when the COX inhibitors were co-administered with each morphine injection during tolerance induction, the dose–response curves of morphine antinociception shifted to the left (Fig. 3). On day 5, the ED_{50} values were 85.12, 17.38 and 22.19 μg for morphine alone, morphine plus NS-398, and morphine plus indomethacin respectively (Table 1). Furthermore, the mean baseline tail-flick latency of morphine-tolerant rats was lower (0.2–1 s) than that of the saline-injected control rats (data not shown).

Discussion

The present study shows that both COX_2-selective and non-selective COX inhibitors attenuated morphine antinociceptive tolerance. No potentiation of morphine antinociception was observed when a COX inhibitor was administered either before or after the development of morphine tolerance. These results suggest that COX is involved in the development of morphine tolerance but does not enhance the antinociceptive effect of morphine.

We found that a selective and a non-selective inhibitor of COX attenuated morphine antinociceptive tolerance. This is consistent with a recent study showing that the non-selective COX inhibitors ketorolac and ibuprofen inhibited the development of morphine tolerance.[22] The morphine-tolerant rats had lower mean baseline tail-flick latency than the control group, suggesting that thermal hyperalgesia may develop in association with the development of morphine tolerance.[10,15] It is interesting that COX$_2$ is not only inducibly expressed after the inflammation process but is also constitutively expressed in the spinal cord of normal rats.[23–25] Furthermore, COX$_2$ is distributed in the superficial layer of the dorsal horn and is related to spinal nociceptive processing in the normal condition.[25] However, it is not clear which COX isoforms are involved in morphine tolerance in the rat spinal cord. The effects of NS-398, a COX$_2$-selective inhibitor, on morphine tolerance and morphine ED$_{50}$ values were slightly greater than those of indomethacin, implying that the inhibition of COX$_2$ may play a role in the development of morphine tolerance. Moreover, the present results agree with those of previous reports showing that COX inhibitors did not produce any thermal antinociceptive effects in the tail-flick test.[21,26] Although the non-selective COX inhibitor ketorolac has been shown to potentiate the analgesic effects of opioids by modulating the function of the opioid receptor in visceral nociception[5], the present results demonstrate that NS-398 and indomethacin did not potentiate morphine antinociception either before or after the development of morphine tolerance. However, these data also confirm that neither COX$_1$ nor COX$_2$ was directly involved in phasic thermal nociceptive transmission in the rat spinal cord.[26]

Our previous studies have demonstrated that several drugs attenuate morphine tolerance and maintain the antinociceptive efficacy of morphine in a rat spinal model.[11,14] Although the non-selective COX inhibitor ketorolac has been shown to potentiate the analgesic effect of opioids by modulating opioid receptor function in visceral nociception,[5] in the present study neither NS-398 nor indomethacin potentiated morphine antinociception, either before or after the development of morphine tolerance. We found previously that the NMDA receptor antagonist MK-801 attenuated morphine tolerance by preventing the reduction of high-affinity μ-opioid receptor sites.[11,14] In the present study, COX inhibitors were found to attenuate morphine tolerance but did not enhance the antinociceptive effect of morphine. Because NMDA receptor antagonists and COX inhibitors shift the morphine dose–response curve in different directions, our present results suggest that COX inhibitors inhibit PG synthesis and related neurotransmission rather than having a direct inhibitory effect on conformational change of the μ-opioid receptor.

In summary, the present results show that COX inhibitors can attenuate the development of morphine tolerance. However, both the non-selective COX inhibitor indomethacin and COX$_2$ inhibitors failed to produce any analgesic effects or potentiation of morphine antinociception either before or after the development of morphine tolerance. Which isoforms of COX are expressed and what interactions occur among the NMDA, NO and COX systems during morphine tolerance in the spinal cord are worthy of further investigation.

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Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure

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The use of a ventilation strategy with high positive end-expiratory pressure (PEEP) that is intended to recruit collapsed alveoli and to prevent recurrent collapse can reduce alveolar protein influx in experimental acute lung injury (ALI). This could affect the pulmonary response to treatment with surfactant, since plasma proteins inhibit surfactant function. We studied the effect of exogenous surfactant on lung mechanics after 4 h of mechanical ventilation with high or low PEEP. Twenty-two adult male Sprague–Dawley rats were anaesthetized, tracheotomized and submitted to pressure-controlled mechanical ventilation with 100% oxygen. One group served as healthy controls (n=6). In the remaining animals acute lung injury was induced by repeated lung lavages to obtain a Pa_{O_2}<13 kPa during ventilation with a peak inspiratory pressure (PIP) of 26 cm H_2O and a PEEP of 6 cm H_2O. These animals were allocated randomly to ventilation with high PEEP (n=8; 100 breaths min^{-1}, I:E=1:1, PIP 35 cm H_2O, PEEP 18 cm H_2O) or to conventional mechanical ventilation (PIP 28 cm H_2O, PEEP 8 cm H_2O; n=8; ventilated control group). After 4 h of ventilation, all animals were given surfactant (120 mg kg^{-1}) via the trachea and ventilation was continued for 15 min. At the end of the study, pressure–volume curves were constructed to measure total lung capacity at 35 cm H_2O (TLC_{35}) and maximal compliance (C_{max}), and bronchoalveolar lavage was then used to measure alveolar protein influx. After lavage, Pa_{O_2} remained around 13 kPa in the ventilated control group and was >66 kPa in the high-PEEP group. After surfactant treatment, Pa_{O_2} increased to >53 kPa in both groups. In the ventilated control group alveolar protein influx was greater and TLC_{35} and C_{max} were lower than in the high-PEEP group. We conclude that the pulmonary response to exogenous surfactant after mechanical ventilation in experimental ALI is improved when a ventilation strategy with high PEEP is used.

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Methods of mechanical ventilation that prevent repeated alveolar collapse are thought to prevent worsening of lung injury during ventilation of surfactant-deficient lungs.[1 2] High positive end-expiratory pressure (PEEP) decreases the accumulation of lung water and protein leakage and prevents intra-alveolar oedema in experimental acute lung injury (ALI).[3–5] A decrease in protein transfer into the alveoli has important consequences for pulmonary function, since proteins inhibit surfactant function in a dose-dependent way.[6] In previous studies in an animal model of ALI, we showed that ventilation with high PEEP attenuated the decrease in lung function, and attributed this effect to a decrease in protein transfer into the alveoli.[3 7]

Exogenous surfactant improves lung function in the respiratory distress syndrome (RDS) of the premature newborn, giving better gas exchange, lung mechanics and outcome.[8] Since hypoxia and poor lung mechanics in ALI are also caused by a lack of active surfactant, the efficacy of surfactant replacement in ALI is being studied experimentally and clinically.[9 10 11] Surfactant therapy in adults is expensive and the large amount of surfactant that is needed is difficult to obtain. If protein influx could be reduced in ALI patients, the surfactant dose could be reduced so that surfactant replacement would be practicable.

We considered the hypothesis that the improvement in lung function after surfactant replacement would be better if

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ventilation with a high PEEP were used to decrease alveolar protein influx. We therefore ventilated surfactant-depleted rats with a high or a low PEEP, and then assessed gas exchange and lung mechanics in response to surfactant treatment.

Methods

The study was approved by the University's animal experiments committee, and the care and handling of the animals conformed with European Community guidelines (86/609/EC). We studied 22 adult male Sprague–Dawley rats (body weight 270–330 g). After induction of anaesthesia with 2% enflurane and 65% nitrous oxide in oxygen, a polyethylene catheter was inserted into a carotid artery to draw arterial blood samples. Before tracheostomy, the animals received 60 mg kg^{-1} pentobarbital sodium i.p. (Nembutal®; Algin, Maassluis, The Netherlands). After tracheostomy, muscle relaxation was induced by pancuronium bromide 1 mg kg^{-1} i.m. (Pavulon®; Organon Teknika, Boxtel, The Netherlands), and the rats were then immediately connected to a ventilator. The animals were mechanically ventilated with a Servo Ventilator 300 (Siemens-Elema, Solna, Sweden) in constant-pressure, time-cycled mode at an inspired oxygen concentration (FI_{O_2}) of 1.0, a frequency of 30 breaths min^{-1} (b.p.m.), a peak inspiratory pressure (PIP) of 12 cm H_2O, a PEEP of 2 cm H_2O, and an inspiratory/expiratory (I:E) ratio of 1:2. Anaesthesia was maintained with pentobarbital sodium 40 mg kg^{-1} h^{-1} i.p.; muscle relaxation was maintained with pancuronium bromide 1 mg kg^{-1} h^{-1} i.m. Body temperature was kept within the normal range with a heating pad. Six animals were killed immediately after induction of anaesthesia and served as healthy controls.

In the remaining animals, acute lung injury was induced by repeated bronchoalveolar lavage (BAL) (32 ml kg^{-1}) with warm saline (37°C).[12] Lavage was repeated as often as necessary to produce a Pa_{O_2} <13 kPa at a PIP of 26 cm H_2O and a PEEP of 6 cm H_2O. Within 10 min after the last lavage, the animals were randomized to two study groups (eight animals in each group). In the first group, mechanical ventilation according to the open lung concept was applied. In this strategy, collapsed alveoli are recruited by applying a high PIP and kept open with a high PEEP, and Pa_{O_2} can be kept >65 kPa.[3] In the present study, we used identical ventilator settings. First, the lungs were opened by increasing PIP to 40 cm H_2O and PEEP to 20 cm H_2O, and the I:E ratio was set at 1:1. After 2–3 min, PIP was decreased to 35 cm H_2O and PEEP to 18 cm H_2O, and arterial blood gas samples were taken. Ventilator settings remained unchanged for the remainder of the study period. In the second group, which served as ventilated controls, ventilator pressure was increased by 2 cm H_2O (PIP/PEEP 28/8 cm H_2O). These ventilator settings were based on results from a previous study using this model, which found that at these settings Pa_{O_2} remained stable at a low value of about 13 kPa for 4 h at an FI_{O_2} of 1.0, indicating that large parts of the lungs remain collapsed and protein transfer into the alveoli is increased.[3] In the present study, both ventilated groups were treated with surfactant at a dose of 120 mg kg^{-1} after 4 h of ventilation. The surfactant used was isolated from minced pig lungs, processed as described previously.[13] The freeze-dried material was suspended in warm saline to a concentration of 40 mg ml^{-1} and given into the trachea after the animals had been disconnected from the ventilator. The surfactant suspension was given as a bolus followed by a bolus of air (12 ml kg^{-1}), directly into the endotracheal tube via a syringe, and this was followed immediately by reconnection to the ventilator. After administration of surfactant, ventilation was continued for 15 min with the previous ventilator settings. This short interval was chosen because maximal improvement of lung function by exogenous surfactant occurs 2–5 min after administration, and because the inactivation of surfactants by proteins occurs instantaneously.

Arterial blood gas samples were taken before lavage, after lavage, hourly for 4 h after lavage, and immediately and 15 min after surfactant administration. The samples were analysed for Pa_{O_2} and Pa_{CO_2} with an electrochemical blood gas analyser (ABL 505; Radiometer, Copenhagen, Denmark).

At the end of the experiment, the animals were killed with an overdose of pentobarbital. Static pressure–volume curves were recorded using conventional techniques. Total lung capacity was defined as lung volume at inflation with a distending pressure of 35 cm H_2O (TLC_{35}). Maximal compliance (C_{max}) was defined as the steepest part of the deflation limb of the pressure–volume curve. After the pressure–volume recordings, BAL was performed five times with saline–$CaCl_2$ 1.5 mmol $litre^{-1}$. The active surfactant component in the BAL fluid was separated from the non-active surfactant component by differential centrifugation followed by subsequent phosphorus analysis, and the ratio of non-active to active components (small aggregate:large aggregate ratio=SA:LA ratio) was calculated as described by Veldhuizen and colleagues.[14] The protein concentration of the BAL fluid was determined using the Bradford method[15] (Bio-Rad, Munich, Germany)

Statistical analysis was performed with the Instat 2.0 biostatistics package (GraphPad, San Diego, CA, USA) under Windows 95. For blood gases, intergroup comparisons were analysed using the alternative (Welch) *t*-test, while intragroup comparisons were analysed using repeated measures analysis of variance (ANOVA). All other data were analysed with ANOVA. If ANOVA resulted in $P<0.05$, a Tukey–Kramer post-test was performed. All data are reported as mean (SD) and $P<0.05$ was considered statistically significant.

Results

Blood gases before and immediately after lavage were similar for the ventilated groups (Fig. 1 and Table 1). None of the animals died during the 4 h and 15 min observation periods. In the group ventilated with high PEEP, Pa_{O_2} increased to the prelavage value and remained stable during the 4 h ventilation period, but decreased to 61.8 (5) kPa after surfactant administration. In the control group, Pa_{O_2} did not improve until surfactant was administered, after which Pa_{O_2} increased to 54.0 (17) kPa.

Pa_{CO_2} data are given in Table 1. In both ventilated groups, Pa_{CO_2} increased after lavage and remained unchanged during the study period (Table 1).

Tidal volume after lavage was similar in the two ventilated groups: 10.2 (0.6) and 10.9 (0.7) ml kg^{-1} for the high-PEEP and control groups respectively.

The protein concentration of BAL fluid was significantly greater in both ventilated groups than in healthy control animals (Fig. 2). However, in the ventilated control group protein concentration was significantly greater than in the high-PEEP group.

There were no differences in SA:LA ratio between the three groups (Table 2). In comparison with healthy control animals, the total amount of phosphorus in the BAL fluid (used to quantify the phospholipid-containing surfactant system) was significantly greater in the groups that received surfactant (Table 2).

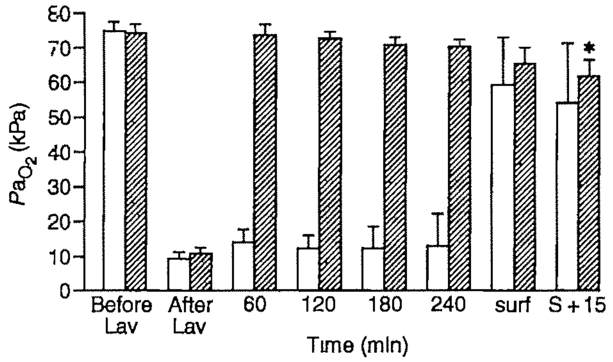

Fig 1 Pa_{O_2} values (mean (SD), kPa) of the ventilated groups. Hatched bars, high-PEEP group; open bars, ventilated control group with low PEEP, Before Lav, before lavage, After Lav, after lavage; surf, after surfactant administration; S+15, 15 min after surfactant administration *P<0.05 versus 240 min.

Table 1 Pa_{CO_2} values (mean (SD), kPa) for the ventilated groups, before lavage (Healthy), immediately after lavage, 60, 120, 180 and 240 min after lavage, immediately after surfactant administration (Surfactant), and 15 min after surfactant administration (Surfactant+15 min). *P<0.05 versus Healthy

	High PEEP	Control
Healthy	4 9 (1 0)	5 0 (0.8)
Lavage	6 7 (0.9)*	7 2 (1.3)*
60 min	7 6 (1.8)*	6.7 (1.6)*
120 min	7 1 (1.5)*	7 0 (1 8)*
180 min	7.5 (1.6)*	7.3 (1 9)*
240 min	7 6 (2 0)*	7 6 (1.6)*
Surfactant	7 1 (2.4)*	7 7 (1 8)*
Surfactant+15 min	7 8 (2.6)*	7.8 (2.1)*

Figure 3 shows the pressure–volume curves. On deflation to 15 cm H_2O, lung volume was less only in the ventilated control group. Below 15 cm H_2O, lung volume in both ventilated groups was less than in the healthy controls. Maximal compliance (C_{max}) was lower in the ventilated control group than in the high-PEEP group and the healthy controls (Table 2).

Discussion

We have shown that surfactant therapy after 4 h of mechanical ventilation can improve total lung capacity and compliance more effectively if ventilation with a high PEEP is used. Protein concentration in the BAL fluid of the high-PEEP group was lower than in the ventilated controls, in which a low PEEP was used.

In the ventilated control group, TLC_{35} and C_{max} were lower than in the healthy controls. In the high-PEEP group this difference was not found (Table 2 and Fig. 3). Surfactant has the unique ability to reduce surface tension at the air–liquid interface in the alveoli and to reduce alveolar radius, thus improving lung distensibility and alveolar stability. Plasma proteins decrease the ability of surfactant to decrease surface tension.[6] We suggest that the poor response of lung mechanics in the low-PEEP group after administration of surfactant was caused by the greater degree of protein transfer into the alveoli in this group. These results are consistent with previous results obtained in this model, in which mechanical ventilation with high PEEP decreased protein transfer into the alveoli and improved lung mechanics.[3 7]

An important factor in decreasing protein influx is probably the prevention of damage to the alveolar epithelium by reducing the shear forces from repeated alveolar collapse.[4] PEEP can also shift fluid from the alveoli to the interstitium by decreasing the pressure gradient across the alveolar–capillary membrane.[16] Furthermore, there is evidence that PEEP prevents the loss of surfactant from the

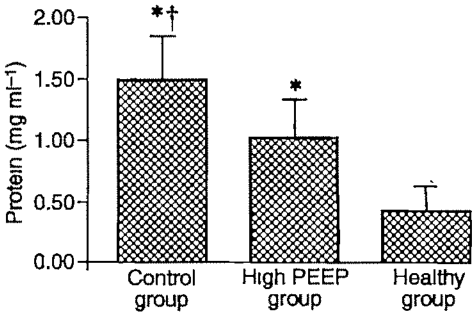

Fig 2 Protein concentration (mean (SD), ml mg^{-1}) of the BAL fluid. *P<0 05 versus healthy controls (Healthy Group); †P<0.05 versus the high-PEEP group Control Group, ventilated controls.

Table 2 Data on maximal compliance (C_{max}, ml cm H_2O^{-1} kg^{-1}), total phosphorus (μmol ml^{-1}) recovered from the BAL fluid, and SA.LA ratio (mean (SD)) *$P<0.05$ versus healthy controls (Healthy), †$P<0.05$ versus high-PEEP group

Group	C_{max}(ml cm H_2O^{-1} kg^{-1})	Total phosphorus(μmol ml^{-1})	SA:LA ratio
Healthy	13.4 (1.1)	0.14 (0.06)	0.31 (0.12)
High PEEP	10.0 (2.6)	0.32 (0.08)*	0.36 (0.17)
Control	6.8 (1.2)*†	0.29 (0.06)*	0.47 (0.19)

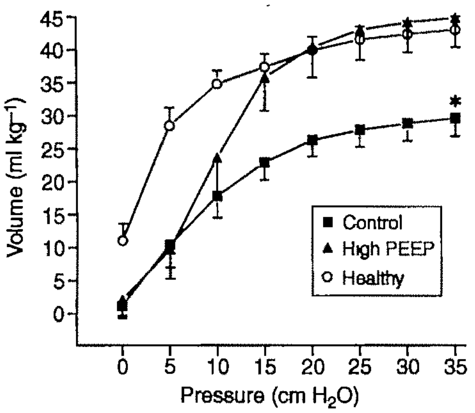

Fig 3 Deflation limbs of the pressure–volume curves (mean (SD)) Volume is lung volume above FRC. On deflation to 15 cm H_2O, lung volume was significantly decreased only in the ventilated control group (Control). Below 15 cm H_2O, lung volume in both ventilated groups was lower than in the healthy controls (Healthy). *$P<0.05$ versus healthy controls.

alveoli. This will prevent an increase in surface tension, which could increase protein influx from capillary to alveolus.[5]

Before administration of surfactant, Pa_{O_2} was >66 kPa in the high-PEEP group, indicating that the ventilator settings were sufficient to open up the lungs and keep them open; this confirms previous experience (Fig. 1).[3 7] The decrease in oxygenation after surfactant administration is attributable to the bolus of liquid in which the surfactant was suspended, which partially filled the alveoli, causing a decrease in diffusion.[9]

No differences were found between the ventilated groups in non-active and active surfactant aggregates (SA:LA ratio). This supports the report of Veldhuizen *et al.*, who showed that the conversion of LA into SA depends on alveolar area cycling and time.[17] Alveolar cycling is determined by tidal volume, which was similar in the two ventilated groups.

An important factor in successful treatment with surfactant in RDS of the premature infant is giving the surfactant shortly after birth, to reduce the time in which proteins can transfer into the surfactant-deficient alveoli. In the adult ALI patient, where the surfactant deficiency is secondary to lung injury, protein concentration in the alveoli is increased.[18] Mixing exogenous surfactant with plasma proteins decreases the ability of surfactant to improve gas exchange, and larger amounts of surfactant are necessary to overcome the inhibitory effects.[6] This study shows that surfactant therapy can be improved by attenuating the increase in protein transfer into the alveoli. It has been suggested that a decrease in alveolar protein concentration, for example by lobe-wise lung lavage, could improve the effect of exogenous surfactant on pulmonary function.[19] Our study suggests that if the lungs are kept open with a high PEEP during the ventilation period before surfactant treatment, the efficacy of surfactant treatment can be improved. Because the inhibition of surfactant by proteins is dose-dependent, a reduction in protein influx during mechanical ventilation before surfactant administration is important, as it could reduce the surfactant dose, reduce costs and improve outcome in ALI.

In conclusion, the improvement in lung function after surfactant treatment in experimental ALI is better if a high PEEP is used to decrease alveolar protein influx. Clinical studies are necessary to assess the effects of high PEEP in ALI patients who might benefit from surfactant therapy, in increasing the efficacy of surfactant replacement and improving the outcome.

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Halothane and desflurane requirements in alcohol-tolerant and -nontolerant rats[†]

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On the basis of data implicating $GABA_A$ receptors in the effects of volatile general anaesthetics, we hypothesized that alcohol-, barbiturate-, and benzodiazepine-sensitive alcohol-nontolerant (ANT) rats would also be more sensitive than alcohol-tolerant (AT) rats to two clinical general anaesthetics with differing potencies, halothane and desflurane. The obtunding effect of halothane and desflurane on mature ANT (n=17) and AT (n=16) rats was assessed by the loss-of-righting reflex endpoint. ANT rats were significantly (P<0.0001) more sensitive to the obtunding effects of both halothane and desflurane (ED_{50}=0.45±0.03% atm for ANT *vs* 0.95±0.04% atm for AT and 2.16±0.17 *vs* 3.69±0.13% atm, respectively). The immobilization effect of halothane and desflurane was assessed with the tail clamp/withdrawal endpoint. ANT rats were more sensitive to the effects of halothane (ED_{50}=1.10±0.08% atm for ANT *vs* 1.72±0.09% atm for AT; P<0.0001) but not desflurane (ED_{50}=6.25±0.25% atm for ANT *vs* 5.85±0.21% atm for AT). The data presented support the hypothesis that volatile anaesthetics interact with specific neuronal proteins (possibly $GABA_A$ receptors) and agree with recent hypotheses that different elements of the anaesthetic state are produced by separate sites or mechanisms.

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γ-Aminobutyric acid type A ($GABA_A$) receptors mediate the postsynaptic actions of the major inhibitory neurotransmitter in mammalian brain. $GABA_A$ receptors are believed to be pentameric combinations of various subunits, of which 16 (α1–6, β1–3, γ1–3, ρ1–2, δ, and ε) have been so far identified.[1] Subunit combinations determine diverse pharmacological $GABA_A$ receptor subtypes in a brain cell- and region-specific manner.[2] Thus, it is possible that various drug actions and behaviours are dependent on certain $GABA_A$ receptor subtypes.

Abundant *in vitro* data demonstrating that structurally heterogeneous general anaesthetics enhance GABA-gated hyperpolarizing currents (reviewed by Tanelian *et al.*[3]) have led to the hypothesis that general anaesthetics act primarily via the $GABA_A$ receptor. One approach to testing this hypothesis is to identify experimental animals with a specific alteration in the genes encoding brain $GABA_A$ receptors and assay for changes in their anaesthetic requirement. Previous investigations have utilized $GABA_A$ receptor mutants arising spontaneously,[4] due to ionizing radiation,[5] or as a result of targeted gene disruption.[6–8] In the case of a spontaneous mutation, a selectively outbred rat line highly susceptible to the motor ataxia produced by alcohol,[9] benzodiazepines and barbiturates is available.[10] The putative underlying mutation involves a single nucleotide substitution in the $GABA_A$ receptor α6 subunit resulting in an $Arg^{100}\rightarrow Gln$ substitution.[11] Given the susceptibility of this rat line, termed alcohol-nontolerant (ANT), to central depressants known to act via the $GABA_A$

[†] Presented in part to the 1995 annual meeting of the Society for Neuroscience (November 12 – 16, 1995, San Diego, CA).

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receptor, we hypothesized that ANT rats would also be cross-sensitive to the actions of volatile general anaesthetics. To test this, anaesthetic requirements were determined in ANT and control, alcohol tolerant (AT) rats, using two volatile agents with widely differing potencies, as well as two separate endpoints reflecting obtundation and immobilization.

Materials and methods

The protocol for these experiments was approved by the Animal Ethics Committee of Helsinki University Central Hospital.

ANT and AT rats are outbred lines derived from crossbred Wistar, Sprague-Dawley, and Long-Evans rats,[9] selected and bred for sensitivity (ANT) or resistance (AT) to ethanol. The selection procedure has been based on motor performance under the influence of a moderate, nonhypnotic dose cf ethanol (2 g kg^{-1}, i.p.). The phenotype is rechecked every second generation. Stocks of AT and ANT rats are kept in stainless steel wire mesh cages on a 12-h light/dark cycle (light on at 6 a.m.) at the ambient temperature (20±2°C) and relative humidity (50±5%). For the present study, male rats of the F_{50} generation were housed four per cage and had continuous access to RMI(E)SQC pellet feed (SDS Ltd, Witham, Essex, UK) and tap water. The age of rats used in this study was 3.5 months (350–430 g).

Six groups (three ANT, three AT) of four to six rats of either genotype (unknown to the observer) were studied during halothane and desflurane anaesthesia, in random order. Each group was placed within a Plexiglas chamber warmed by heating pads from below and an infrared lamp from above. The composition of the chamber's atmosphere was monitored continuously on-line with Datex Capnomac Ultima™ and Normac™ devices (for oxygen/carbon dioxide, and volatile anaesthetic concentrations, respectively). Fresh oxygen flow was delivered via a Dameca oxygen vernitrol at rates of 1.5–8 litres min^{-1}. Volatile agents were added to the fresh gas stream by means of either a Fluotec 3™ (Cyprane Ltd, Keighley, UK) or an Ohmeda Tec 4™ vaporizer (Ohmeda, Inc., Steeton, West Yorkshire, UK). Carbon dioxide concentration was maintained at <1.0% atm by means of soda lime scattered on the floor of the chamber.

After a 20-min equilibration period at a given anaesthetic concentration, rats were gently placed supine and observed for the ability to roll over spontaneously to the fully prone position within 30 s. Responses were scored in a quantal fashion. Immediately thereafter, the base of the tail of each rat in the group was clamped with a full-sized Kelly haemostat to the second ratchet position, and gross withdrawal within 5 s scored quantally. Withdrawal was defined as jerking of the head, twisting of the neck, or movement of an extremity; coughing, swallowing, chewing, and grimacing motions were not scored as positive responses, nor were increases in the respiratory rate.[12] Rectal temperatures were then measured using a digital thermometer (Exacon MC8700, Denmark) with an accuracy of ±0.1°C. The rats were allowed to recover in an oxygen-rich atmosphere for at least 20 min before they were equilibrated with the next higher anaesthetic concentration and retested for both the obtundation and immobilization endpoints. For both agents, 9–13 different concentrations were tested in each group of rats.

After all experiments were completed, halothane and desflurane response data from the three ANT groups (*n*=17 rats) or three AT groups (*n*=16 rats) were pooled. The dose-response relationships were analysed by fitting to a logistic equation,[13] which yielded estimates of the ED_{50} and slopes for each agent, as well as their respective standard errors. The ANT and AT group responses were then compared, using a method making the fewest assumptions about the distribution of errors.[14] Briefly, the estimated variances for the AT and ANT groups were calculated from the standard errors; the sum of these then yielded the estimated variance of the difference in ED_{50} between groups. The ratio of this difference to its standard error was referred to a standard normal distribution.

Table 1 Halothane requirements* in AT and ANT rats as measured by loss of righting reflex and withdrawal following tail clamp stimulus. *Median effective doses (ED_{50}, expressed in % atm), dose-response curve slopes, and their respective standard errors (SE) are listed for individual experiments. Results of refitting combined data from triplicate experiments are also shown. $^{\dagger}P<0.0001$ *vs* AT ED_{50}. $^{\ddagger}P>0.49$ *vs* AT slope. $^{\S\S}P<0.0001$ *vs* AT ED_{50}. $^{\P\P}P=0.10$ *vs* AT slope

Experiment	***n***	**Loss of righting reflex** **ED_{50}**	**±SE**	**-Slope**	**±SE**	**Tail clamp/withdrawal** **ED_{50}**	**±SE**	**-Slope**	**±SE**
AT rats									
1	4	1.07	0.09	9.3	4.1	Not able to fit			
2	6	0.79	0.05	0.7	4.1	1.72	0.07	11.0	3.3
3	6	1.09	0.05	13.1	4.5	1.69	0.06	14.2	4.3
Combined	16	0.95	0.04	7.7	1.5	1.72	0.09	12.2	2.2
ANT rats									
1	6	0.41	0.79	6.6	8.5	1.08	0.07	9.3	2.9
2	6	0.47	0.06	5.0	1.6	1.25	0.07	9.6	3.0
3	5	0.41	0.05	6.3	2.6	0.96	0.07	9.1	3.1
Combined	17	$0.45^{\dagger}$	0.03	$6.3^{\ddagger}$	1.4	$1.10^{\S\S}$	0.08	$8.2^{\P\P}$	1.4

Results

Halothane- and desflurane-induced obtundation and immobilization were reversible in all rats from both the AT and ANT groups. Rectal temperatures were maintained throughout the experiments to within 1.5°C of the mean value obtained after each dose was tested in a given group.

Data obtained during halothane anaesthesia are summarized in Table 1 and Figures 1 and 2. These six experiments included three with AT rats (n=16) and three with ANT rats (n=17). For each genotype/endpoint combination, the arithmetic mean of the ED_{50} values obtained separately closely agreed with the ED_{50} obtained by a free fit of pooled data (for example, 0.98 *vs* 0.95% atm, respectively, for AT rats tested by loss-of-righting-reflex).

Results from all individual experiments with desflurane are summarized in Table 2 and Figures 3 and 4, including three experiments each with AT (n=15) and ANT (n=15) rats. Again, means of the separate ED_{50} values agreed with the values from pooled data.

Since the slopes (Tables 1 and 2) of the pooled loss-of-righting-reflex data for the AT vs ANT groups were not significantly different (P>0.49 for halothane; P>0.25 for desflurane), it is valid to compare the ED_{50}s for those groups. Halothane sensitivity in the AT line (0.95±0.04% atm) was less than previously reported values in wild-type mice (generally 0.6–0.7% atm),[6,8,15] but ANT rats (0.45±0.03% atm) were more sensitive than previous reports. No previous reports of desflurane sensitivity in the loss-of-righting reflex assay in rodents are available for comparison. For both agents, the ANT rats were significantly more sensitive with respect to obtundation than AT rats (P<0.0001 for halothane; P<0.0001 for desflurane) (Tables 1 and 2). The magnitude of the difference in sensitivity was slightly greater for halothane (ANT ED_{50} equal to 47% of the AT value) than for desflurane (ANT ED_{50} equal to 58% of the AT value).

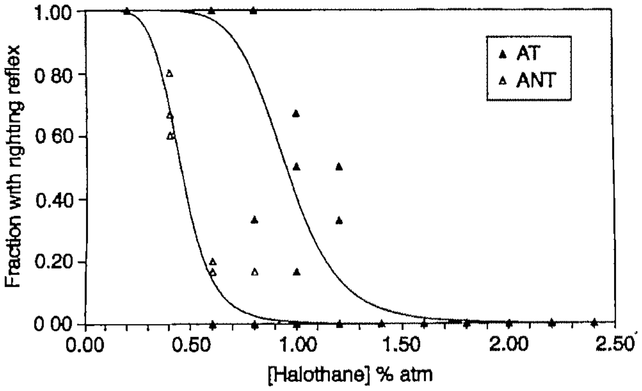

Fig 1 Halothane requirements in ANT *vs* AT rats defined by the endpoint of loss of righting reflex Data from six separate experiments are plotted· each data point is the fractional response of the group (four to six rats) to a given halothane concentration. Curves are derived as in Materials and methods.

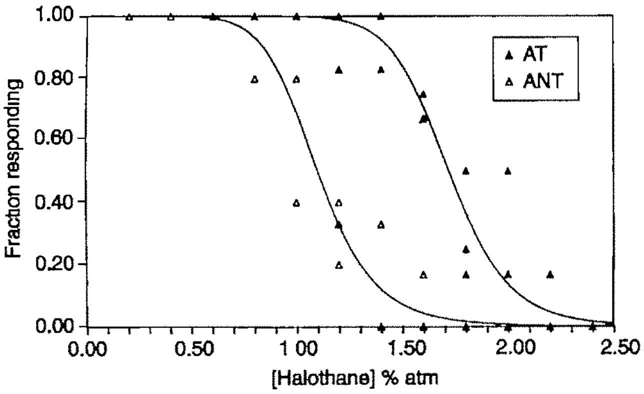

Fig 2 Halothane requirements in ANT *vs* AT rats defined by withdrawal following a tail clamp stimulus. Data and curve fitting as in Figure 1.

Similarly, the slopes of the pooled tail clamp/withdrawal data for the AT *vs* ANT groups were not significantly different (P>0.10 for halothane; P>0.15 for desflurane). Halothane sensitivity in the AT line (1.72±0.09% atm) was again less than that previously reported for MAC in wild-type rats (approximately 1–1.2% atm), while the ANT value (1.1±0.08% atm) was similar to previous reports. Desflurane ED_{50} values for tail clamp for both AT (5.85±0.21% atm) and ANT (6.25±0.25% atm) lines were within the range of previous reports in rats (5.7–6.8% atm).[16,17] Comparison of the ED_{50} values for these groups showed that for halothane, the ANT rats were significantly more sensitive than were AT rats with respect to the immobilization endpoint (P<0.0001), but ANT and AT rats had similar sensitivity to the immobilizing effects of desflurane (P>0.50).

Discussion

ANT rats were originally bred for their sensitivity to alcohol[9] and subsequently were found to be cross-sensitive to benzodiazepines and barbiturates.[10] In the present study, we hypothesized that ANT rats would also exhibit cross-sensitivity with volatile anaesthetics.

We found that ANT rats were significantly more sensitive than AT rats to the obtunding effects of halothane and desflurane. ANT rats were also more sensitive to the immobilizing effects of halothane, but not desflurane. This inconsistent response to desflurane is unlikely to be anomalous, since our measurement of tail-clamp ED_{50} for desflurane in AT rats (5.85±0.21% atm) agreed closely with the minimum alveolar concentration (MAC) of desflurane in oxygen reported in normothermic Sprague-Dawley rats (5.72±0.40% atm).[14] It is also unlikely that the immobilization assay result with desflurane was an artefact of the group sizes studied: a 20% difference between ED_{50} values would have been detectable in these groups by the statistical methods employed. Instead, this nonuniformity of response to the volatile agents more likely indicates that the immobilizing effect has different neuronal and neurochemical mechanisms than does the obtunding effect. Therefore,

Table 2 Desflurane requirements* in AT and ANT rats as measured by loss of righting reflex and withdrawal following tail clamp stimulus *Median effective doses (ED_{50}, expressed in % atm), dose-response curve slopes, and their respective standard errors (SE) are listed for individual experiments. Results of refitting combined data from triplicate experiments are also shown †$P<0.0001$ *vs* AT ED_{50} ‡$P>0.25$ *vs* AT slope ‖$P>0.50$ *vs* AT ED_{50} ¶$P>0.15$ *vs* AT slope

		Loss of righting reflex				Tail clamp/withdrawal			
Experiment	*n*	**ED_{50}**	±SE	-Slope	±SE	**ED_{50}**	±SE	-Slope	±SE
AT rats									
1	6	3.62	0.12	7.5	2.0	5.60	0.18	17.0	5.8
2	4	3.35	0.24	10.9	3.9	6.09	0.16	24.8	9.9
3	5	4.03	0.19	10.8	3.3	5.87	0.16	19.3	6.3
Combined	15	3.69	0.13	8.4	2.7	5.85	0.21	17.6	7.0
ANT rats									
1	6	2.19	0.30	3.5	0.8	6.35	0.22	20.1	10.3
2	4	2.48	0.30	5.8	2.1	6.14	0.46	9.0	4.1
3	5	1.91	0.23	6.0	2.3	5.66	0.31	9.4	3.2
Combined	15	2.16†	0.17	4.2‡	0.7	6.25‖	0.25	11.9¶	4.6

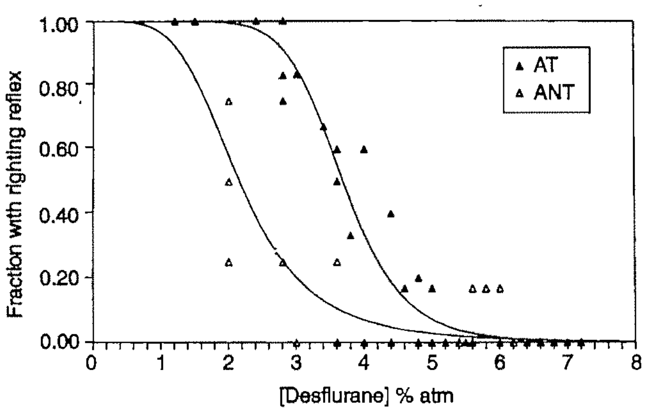

Fig 3 Desflurane requirements in ANT *vs* AT rats defined by the endpoint of loss of righting reflex Data and curve fitting as in Figure 1.

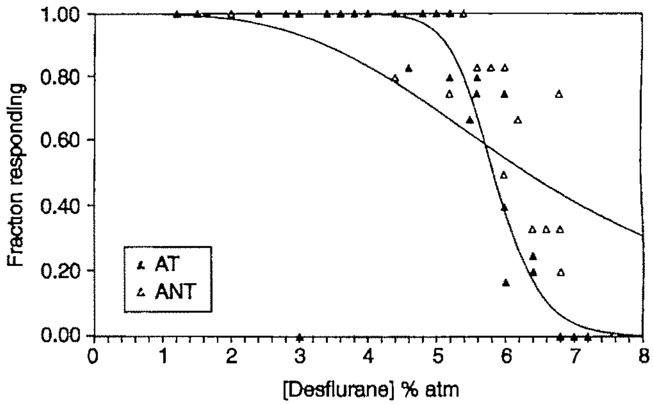

Fig 4 Desflurane requirements in ANT *vs* AT rats defined by withdrawal following a tail clamp stimulus. Data and curve fitting as in Figure 1.

these data agree with the hypothesis that separate elements of the anaesthetic state are produced by independent mechanisms.[18] The oil/gas partition coefficient of halothane is about 12 times greater than that of desflurane.[19] The relatively greater lipid solubility of halothane allows for the possibility that halothane interacts with more hydrophobic regions of the membrane surrounding the $GABA_A$ or another receptor.[20]

ANT rats were first noted to display unusual cerebellar $GABA_A$ receptor binding pharmacology,[21] which were subsequently proven to have a point mutation in the N-terminal extracellular portion of the α6 subunit.[11] This α6 subtype is expressed almost exclusively in cerebellar granule cells,[22] which are intrinsic to the cerebellar cortex and are the most ubiquitous neuron found in the mature mammalian nervous system. The role of cerebellum in motor coordination, posture maintenance, balance, and muscle tone is clear,[23] but its role in conscious behaviours, including motor learning, is currently an area of intense research (reviewed by Glickstein).[24] Classically, granule cells relay information between cerebellar input (mossy fibre) and output (Purkinje) neurons. The α6 subunit-containing $GABA_A$ receptor is among the most sensitive subtype to inhibition by GABA;[25] thus, potentiation of GABA actions at granule cells by an anaesthetic could sharply reduce Purkinje cell output from the cerebellar cortex to the deep cerebellar nuclei, and subsequently to the brain. Indeed, attenuation of Purkinje output could explain, at least in part, the motor ataxia of intoxicated ANT rats, but might not be critical for deep anaesthesia.

In vitro, some anaesthetics (propofol and trichloroethanol) have significantly lower efficacy, but not apparent affinity, at α6 subunit-containing $GABA_A$ recombinant receptors expressed in cell lines, as compared with those containing the α1 subunit.[26] However, pentobarbital potentiates GABA-gated currents more significantly in α6-containing cells than in those containing α1.[27] The significance of these findings *in vivo* remains to be determined. Studies of mice with α5 and γ3 $GABA_A$ receptor gene deletions suggest that these subtypes are not essential for the halothane response.[5] In contrast, targeted gene disruption of the β3 subunit of the $GABA_A$ receptor increases halothane and enflurane MAC but not the ED_{50} for loss of righting.[8]

Despite extensive characterization of the ANT α6 $GABA_A$ receptor genotype, there is still a possibility that other mutations coexist in ANT rats that affect the central nervous system.[28] Additional but unidentified mutations could, in principle, have become enriched in the selected population along with the defective $\alpha 6$ gene and be the actual basis for the drug-response phenotype reported here. The role of possible unidentified mutations could be assessed in crossbreeding experiments in which AT rats are mated with ANT, siblings of the first generation are mated again, and anaesthetic sensitivity is determined in this resulting generation of rats. The degree of dominance of the $\alpha 6$ mutation should determine the distribution of anaesthetic sensitivity in rats of the second generation. However, such experiments are costly and require large numbers of animals. Additional unidentified mutations may be excluded by using targeted disruption, or site-specific alteration, of the gene in question. Such an approach was recently used to establish that the $GABA_A$ $\gamma 2$ receptor subunit is essential to benzodiazepine agonist action *in vivo*; targeted disruption of the subtype gene by homologous recombination resulted in mice for whom diazepam was behaviourally inactive.[7] Mice completely lacking the $\alpha 6$ subunit, created using similar techniques, do not differ from wild type mice in their sensitivity to either halothane or enflurane in the loss-of-righting reflex assay or the tail clamp assay.[6] These mice also exhibit normal responses to ethanol and pentobarbital[6 29] but their response to the motor ataxic effects of diazepam was enhanced.[29] The dramatic difference in the pharmacological profile of rats with an intact but altered $\alpha 6$ subunit and null allele mice completely lacking any $\alpha 6$ subunits suggests that other undocumented mutations in the ANT line may be responsible for at least some of their abnormal behavioural responses, but the difference could also be explained by substitution of other subunits for the missing $\alpha 6$ subunits in the null allele mice.[6] An alternative explanation is that the $\alpha 6$ null allele is pharmacologically and behaviorally very different from the gain of function mutation that is present in the ANT rat line.

In conclusion, we have documented that the obtunding effects of halothane and desflurane are markedly enhanced in ANT rats compared to AT controls. The immobilizing effects of halothane, but not desflurane, were also enhanced in the ANT rat line. Since ANT rats are known to contain a point mutation in the $\alpha 6$ subunit of the $GABA_A$ receptor that segregates with the ANT phenotype, it is tempting to speculate that the enhanced behavioral sensitivity to the volatile agents is also due to this mutation. However, it is equally plausible that an additional mutation(s) is the basis for the observed phenotype.

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REVIEW ARTICLE

The aged cardiovascular risk patient

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Keywords: age factors; cardiovascular disease

There is no precise definition of 'the aged', 'the elderly' or 'advanced age'. This is hardly surprising, because there is no specific clinical marker of the 'geriatric' patient, and ageing does not occur abruptly but represents a continuum. In fact, the 'geriatric population' is unique for its non-homogeneity: physical and medical heterogeneity increase with advancing age.[78] Nevertheless, data analysis by age quintiles supports the clinical relevance of usually defining patients aged >64 yr as the elderly cohort.[1] Approximately 15% of the Western population,[35 44] and about 25% of surgical patients[98] are aged ⩾65 yr. Half of these will undergo surgery in the remainder of their life time.[98]

Age itself is an independent morbidity and mortality risk factor for a long list of diseases and injuries, hospitalization, length of hospitalization, and adverse drug reactions.[16] With very few exceptions,[10 88] age has been shown to be an independent predictor of perioperative outcome.[3 5 17 19 53] If we are to successfully reduce age-related perioperative cardiovascular morbidity and mortality (the main contributor to overall adverse perioperative outcome[68]) we need to define the factors that increase perioperative cardiovascular risk age-dependently. Although we might not always be able to improve underlying conditions, awareness of such additional risk factors may modify our perioperative anaesthetic management in a way that will ultimately improve outcome.

Accordingly, this review will first address the question of what constitutes perioperative cardiovascular risk, independent of age. It will then focus on factors that might affect perioperative cardiovascular outcome age-dependently. Such factors include age-related changes in cardiovascular structure and function, altered cardiovascular response to increased flow demands in the elderly, coexisting cardiovascular and other disease with advancing age, and drug therapy in older people. Finally, anaesthetic implications will be discussed.

Cardiovascular risk assessment

The preoperative assessment of perioperative cardiovascular risk relies on the evaluation of clinical markers, functional capacity and surgery-specific risk. On the basis of such evaluation, different levels of risk can be defined.[43]

Clinical markers

Clinical markers of increased perioperative cardiovascular risk for myocardial infarction, congestive heart failure and death can be placed in three categories: major, intermediate and minor predictors (Table 1). In conjunction with the concomitant degree of functional capacity and the anticipated surgical risk, the severity of the clinical marker will influence the subsequent perioperative management (see below).[43]

Functional capacity

In clinical practice, exercise tolerance in daily life ('medical' or 'physical fitness') best reflects the 'quality' of biological age. It is one of the most important predictors of perioperative outcome in the elderly surgical patient.[43 88] Poor exercise tolerance may reflect the severity of the underlying disease, or a lower functional capacity. Functional status can be expressed in metabolic equivalent (MET) levels. One MET corresponds to the oxygen consumption ($\dot{V}O_2$) of a 70 kg, 40 yr old man in a resting state, which is approximately 3.5 ml kg^{-1} min^{-1}. Multiples of the baseline 1 MET value can be used to define the aerobic demands for specific activities (Table 2). Functional capacity is assessed by recording daily activities, and has been classified as excellent (>7 METs), moderate (4–7 METs), poor (<4 METs) or unknown.[30 46] Such a clinical questionnaire provides an estimate, but not an objective measurement of functional status (such as exercise testing).

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Table 1 Clinical predictors of increased perioperative cardiovascular risk (adapted from reference 43)

Major predictors	unstable coronary syndromes, decompensated congestive heart failure, significant arrhythmias, severe valvular disease
Intermediate predictors	mild angina pectoris, previous myocardial infarction (>30 days old), compensated or previous congestive heart failure, diabetes mellitus
Minor predictors	advanced age, abnormal ECG, rhythm other than sinus, low functional capacity, history of stroke, uncontrolled systemic hypertension

Table 2 Estimated energy requirements for various activities (adapted from reference 43)

	Can you ..
1 MET	take care of yourself?
↓	eat, dress or use the toilet?
	walk indoors around the house?
	walk a block or two on level ground at 2–3 mph (3.2–4 8 km h^{-1})?
	do light work around the house, like dusting or washing dishes?
4 METs	climb a flight of stairs or walk up a hill?
↓	walk on level ground at 4 mph (6.4 km h^{-1})?
	run a short distance?
	do heavy work around the house, like scrubbing floors or lifting or moving heavy furniture?
	participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
>10 METs	participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?

Table 3 Perioperative cardiac risk (combined incidence of cardiac death and nonfatal myocardial infarction for noncardiac surgical procedures) (adapted from reference 43)

Risk of procedure	Examples
High (often >5%)	emergent major operations, particularly in the elderly; aortic and other major vascular; peripheral vascular; anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss
Intermediate (generally <5%)	carotid endarterectomy; head and neck; intraperitoneal and intrathoracic, orthopaedic; prostate
Low (generally <1%)	endoscopic procedures, superficial procedures; cataract; breast

Patients unable to meet a 4 MET demand during most normal daily activities have increased perioperative short-term and long-term cardiac risk.[43]

Surgery-specific risk

It appears obvious that different surgical procedures would be associated with different cardiac outcome. Surgery-specific cardiac risk is related to two factors: type of surgery and degree of haemodynamic cardiac stress associated with a particular surgical procedure. Examples of high-risk (combined perioperative incidence of myocardial infarction and/or death ⩾5%), intermediate-risk (reported cardiac risk generally <5%) and low-risk procedures (reported cardiac risk generally <1%) are listed in Table 3.

Advanced age

The *Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery* of the American College of Cardiology and the American Heart Association[43] are somewhat ambiguous as to the clinical significance of advanced age as an independent risk factor. Being listed as a minor clinical predictor would imply that advanced age has not been proven to increase perioperative cardiac risk independently (the definition provided for the category of minor clinical predictors). However, the very same guidelines also state that high-risk surgical procedures include 'emergent major operations, particularly in the elderly', and that 'advanced age is a special risk'.[43] Such a statement implies that advanced age does, in fact, present an independent predictor of perioperative cardiac outcome.

Various combinations of major, intermediate or minor clinical predictors, of excellent, moderate or poor functional capacity, and of high-risk, intermediate-risk or low-risk surgical procedure will predict the overall extent of perioperative cardiovascular risk. Obviously, the old patient with major clinical predictors and poor functional capacity undergoing a high-risk surgical procedure carries the highest perioperative cardiac risk.

Age-related cardiovascular changes

Heart

Ageing is associated with numerous molecular, ionic, biophysical and biochemical changes in the heart.[31 61 63] These changes affect protein function, mitochondrial oxidative phosphorylation, Ca^{2+} kinetics, excitation–contraction coupling, myofilament activation, contractile response, matrix composition and regeneration, cell growth and size, and apoptosis (Table 4).[61]

Age-related changes in cardiac morphology (Table 5) are mostly the result of alterations of intracellular molecular and biochemical pathways. In turn, many of the changes in cardiac function (Table 5) with advancing age develop in response to underlying alterations in morphology. Ultimately, cardiac ageing results in decreased mechanical and contractile efficiency, prolongation of the relaxation phase, stiffening of myocardial cells, mural connective tissue and valves, decreased number of myocytes, increased myocyte size, increased rate of myocyte apoptosis and blunted β-adrenoceptor-mediated contractile and inotropic response.[37 62 76 111]

Vasculature

Ageing affects various aspects of vascular morphology and function (Table 6).[59–61 106] The large arteries dilate, their walls thicken, the wall matrix changes, elastolytic and collagenolytic activity increases and smooth muscle tone increases.[42 59 61] As a result, vascular stiffness increases with advancing age.[59 61]

Cardiac adaptations

Increased vascular stiffness leads to elevated systolic arterial pressure and pulse-wave velocity, and to early reflected pulse pressure waves and late peak systolic pressure, thereby augmenting aortic impedance and cardiac mechanical load (Fig. 1).[63] In this way, arterial stiffening triggers a variety of cardiac adjustments. Some of these adjustments are additional and are similar to the age-related intrinsic changes in cardiac morphology and may, therefore, be expected to worsen cardiac performance.

Table 4 Age-related changes in cardiac cellular and biochemical mechanisms in experimental animals

Isomyosin shift
Expression of fibrosis-related genes
Altered growth-controlling factors
Impaired excitation–contraction coupling
Impaired calcium homeostasis
Increased myocyte apoptosis
Increased atrial natriuretic peptide secretion

The chronically elevated left ventricular afterload ultimately causes left ventricular wall thickening,[55] which is largely a result of an increase in the size of cardiac myocytes.[76] The combination of late augmentation of aortic impedance (through early reflected pulse waves) and left ventricular hypertrophy (partly adaptive) prolongs myocardial contraction. The prolonged myocardial contraction time could contribute to preserved left ventricular pump function, as it prolongs the time available to eject blood from the heart into the stiffened vasculature.

On the other hand, prolonged myocardial contraction delays ventricular relaxation at the time of mitral valve opening, as reflected by reduced early left ventricular filling rate in older individuals.[37 79 93] Early diastolic filling rate declines by approximately 50% between 20 and 80 yr of age.[63] In addition to the purely mechanical reason (i.e. prolonged contraction time), the decrease in early diastolic filling rate may, in part, be caused by a prolonged isovolumetric relaxation time between aortic valve closure and mitral valve opening, possibly because of a reduced rate of Ca^{2+} sequestration from the myoplasm to the sarcoplasmic reticulum.[61]

An increase in late diastolic filling partly compensates for the decrease in early diastolic filling rate and helps to maintain end-diastolic volume and stroke volume in the elderly.[61] However, this compensatory mechanism is dependent on the effective atrial contribution to late diastolic filling. The importance of atrial activity is reflected by an age-related increase in left atrial size[55] and enhanced atrial contribution to late ventricular filling.[37] The latter explains the greater dependency of stable haemodynamics on sinus rhythm with advancing age. Left atrial enlargement may contribute to the greater likelihood of lone atrial fibrillation in the elderly.

In ageing men, an elevated end-diastolic volume maintains cardiac output by increasing stroke volume in the

Table 5 Age-related changes in cardiac morphology and function

Morphology	decrease in myocyte number, increase in myocyte size, decrease in matrix connective tissue, increase in left ventricular wall thickness, decrease in conduction fibre density, decrease in sinus node cell number
Function	decrease in intrinsic contractility, increase in myocardial contraction time, decrease in myocardial contraction velocity, increase in myocardial stiffness, increase in ventricular filling pressures, increase in left atrial pressure/size, increase in action potential time, decrease in coronary flow reserve, decrease in β-adrenoceptor-mediated modulation of inotropy and chronotropy

Table 6 Age-related changes in vascular morphology and function

Morphology	increase in diameter and stiffness of large elastic arteries, increase in medial and intimal thickness, increase in endothelial variant cells, increase in elastolytic and collagenolytic activity, change in vascular cell proliferation/migration, change in vascular wall matrix
Function	decrease in β-adrenoceptor, flow-dependent, endothelium-dependent and atrial-natriuretic-peptide mediated vasodilation, decrease in nitric oxide production/effect, increase in vascular impedance, increase in pulse wave velocity, early reflected pulse waves

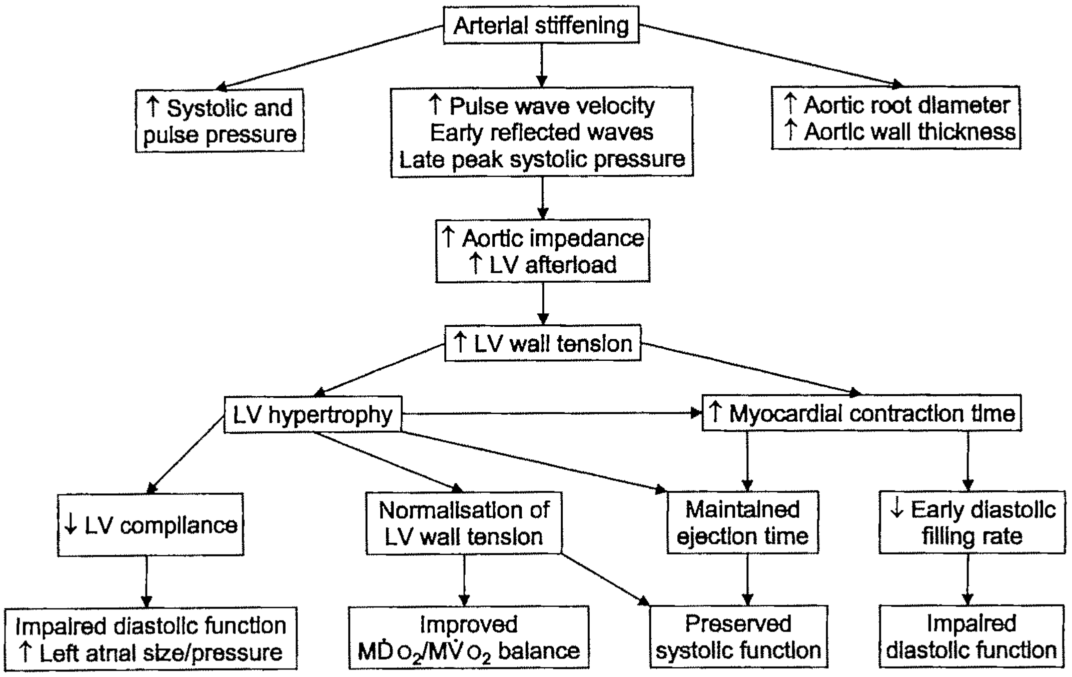
Arterial stiffening
↑ Systolic and pulse pressure
↑ Pulse wave velocity
Early reflected waves
Late peak systolic pressure
↑ Aortic root diameter
↑ Aortic wall thickness
↑ Aortic impedance
↑ LV afterload
↑ LV wall tension
LV hypertrophy
↑ Myocardial contraction time
↓ LV compliance
Normalisation of LV wall tension
Maintained ejection time
↓ Early diastolic filling rate
Impaired diastolic function
↑ Left atrial size/pressure
Improved MḊO₂/MV̇O₂ balance
Preserved systolic function
Impaired diastolic function

Fig 1 Cardiac adjustments to arterial stiffening during ageing. LV=left ventricular. $\dot{M}D_{O_2}$=myocardial oxygen supply. $M\dot{V}_{O_2}$=myocardial oxygen demand.

Table 7 Changes in cardiovascular physiology in healthy individuals at rest between the ages of 20 and 80 yr, LV=left ventricular (adapted from reference 61)

LV end-diastolic volume	increases (c.20%) in males, no change in females
LV end-systolic volume	increases (c 20%) in males, no change in females
Ejection fraction	no change
Stroke volume	increases (c.20%) in males, no change in females
Heart rate	decreases (c.10%)
Cardiac output	no change in males, decreases (c.15%) in females
Stroke work	increases (c 15%)
Early diastolic filling rate	decreases (c.50%)
Systolic arterial pressure	increases (c.15%)
Systemic vascular resistance	no change in males, increases (c.45%) in females

presence of an age-related decline in heart rate (Table 7).[61] As there is no comparable increase in end-diastolic volume in women, cardiac output decreases modestly in ageing females.[28]

The heterogeneity in filling among left ventricular segments increases with age.[8] The normal ageing process seems to have similar effects on right and left ventricular diastolic performance.[55] At rest, mild diastolic dysfunction has little adverse effect on systolic myocardial performance in healthy elderly people,[28 61] as reflected by maintained ejection fraction, stroke volume and stroke work, and only marginally elevated end-systolic volume in men (Table 7).[28] At times of cardiovascular stress, however, the limited cardiac reserve capacity of the elderly becomes apparent (see below).

An age-related increase in left ventricular systolic stiffness (as determined by the end-systolic elastance, E_{es}) seems to accompany the age-related increase in vascular stiffness (as determined by the effective arterial elastance, E_a), even in the absence of cardiac hypertrophy.[14] Comparable increases in E_a and E_{es} with age maintain the E_a/E_{es} ratio,[14] an index of ventricular–arterial coupling. Ageing increases E_a principally by its effects on pulsatile loading, with an additional but smaller age-dependent effect from mean resistance.[14 34]

Although the increase in E_{es} maintains the E_a/E_{es} ratio with age, the increase in both parameters imposes a limitation on net ventricular–arterial interaction, in as much as systolic arterial pressure becomes more sensitive to changes in ventricular filling. Even small blood volume shifts from heart to peripheral vessels can result in considerable changes in arterial pressure.[14]

Since contractile reserve is also linked to increases in E_{es}, age-related elevation of baseline E_{es} might limit some of this contractile reserve and may contribute to the blunting of end-systolic volume decline during exercise (see below).[28]

Furthermore, the age-related increase in ventricular stiffness may contribute to the increased prevalence of hypotension with normal physiological stresses like postural shift,[77] and enhanced pressure changes with excess sodium intake or restriction[107] and diuretics.[73] Thus, ventricular and arterial stiffening may well amplify the adverse effects of diastolic, autonomic and baroreflex dysfunction (see below) on cardiovascular compensatory mechanisms.

Coronary circulation

Ageing is associated with structural and functional changes in the coronary vasculature, which could affect myocardial perfusion with advancing age. The gradual age-related decline in coronary flow reserve may be a result of elevated baseline cardiac work and myocardial blood flow[18] or abnormal vasodilator capacity. Such a reduced dilator reserve may be the result of impaired endothelium-dependent dilation of large epicardial and resistance coronary vessels,[25] decreased basal and stimulated release of nitric oxide by the coronary endothelium,[2] or increased coronary vasoconstrictor effect of endothelin-1 (ET-1).[41] Endothelin plasma concentrations increase with increasing age.[71]

Autonomic nervous system

Ageing is accompanied by a variety of neurohumoral changes (Table 8). Increased basal sympathetic outflow[23] and norepinephrine plasma concentrations[26] suggest an upregulation of sympathetic outflow.[23] Such sympathetic overactivity leads to desensitization of β-adrenoceptors, which may account for the blunted postsynaptic responsiveness to β-adrenergic stimuli with ageing.[61 64 109]

Whereas the vasodilatory response to β-adrenoceptor stimulation decreases with age, the contractile response to α-adrenoceptor stimulation appears to be unaltered, or may even increase with age. The precise mechanism for this observation remains uncertain. It may be related to an age-related increase in arterial (but not venous) α_1-adrenoceptor density.[90]

Ageing affects autonomic cardiovascular control mechanisms in different ways.[94 109] Attenuated respiratory sinus arrhythmia with advancing age[23 56] suggests a decrease in parasympathetic influence on sinus node function. Age-related increases in catecholamine plasma concentrations[26] and in the basal rate of sympathetic neural firing[23] reflect increased sympathetic nerve activity and suggest blunted sinoaortic baroreflex sensitivity that reduces the restraint on sympathetic outflow. Preservation of the sympathetic limb of the baroreflex (i.e. sympathetic reflex response to changes in the peripheral circulation) with advancing age[23] would suggest reduced tonic baroreceptor function (i.e. less inhibitory afferent signals at a given arterial pressure) but maintained gain during arterial pressure pertubations. In contrast, the heart rate reflex response to alterations in arterial pressure is clearly impaired with advancing age.

Table 8 Age-related neurohumoral changes

Sympathetic nerve activity increases
Parasympathetic nerve activity decreases
Plasma catecholamine concentration increases
Baroreceptor reflex activity decreases
β-Adrenoceptor responsiveness decreases
α_1-Adrenoceptor responsiveness increases (?)

Age-related autonomic and baroreflex dysfunction may compromise arterial pressure homeostasis in response to diuretic therapy, altered fluid intake and postural stress.[97 107] Age-related changes in heart rate response to posture, hypotension and various other physiological stimuli have also been reported.[15] Blunted baroreceptor reflex response may contribute to sinus node depression, carotid sinus syndrome and syncope in the elderly.

Response to increased oxygen demand

The haemodynamic response to cardiovascular stress is influenced by various factors, including the nature of the cardiovascular stimulus, the posture in which the cardiovascular system is challenged, gender, fitness and cardiovascular health. Besides these factors, age plays a significant role.[28 75 112]

In healthy, sedentary individuals, maximum work capacity and oxygen consumption ($\dot{V}o_{2max}$) decrease by approximately 10% per decade after the age of 20 yr.[61] At a given $\dot{V}o_{2max}$, increases in heart rate and ejection fraction, and peripheral vasodilation are blunted in the elderly. The decrease in maximum physical capacity may not result solely from limitations in the central circulation (i.e. cardiac reserve capacity), but may also be related to peripheral factors (i.e. redistribution of blood to working muscles, impaired ability of muscle to extract and use oxygen).[27 61] The cardiac element of the diminished $\dot{V}o_{2max}$ in healthy individuals is caused primarily by an age-related decline in the maximum heart rate.[28 92]

One of the major age-associated alterations in the cardiovascular response to exercise is a striking decrease in heart rate and contractile response, as reflected by decreases in peak heart rate and peak ejection fraction, and by a progressively blunted exercise-induced decrease in end-systolic volume with advancing age (Table 9).[28] The Frank–Starling mechanism is the major mechanism that maintains stroke volume in the elderly: peak end-diastolic volume during exercise increases progressively with advancing age and is considerably (*c*.30%) larger in old than in young individuals (Table 9).[28] The augmentation of end-diastolic volume preserves stroke volume but attenuates the increase in ejection fraction.[28]

The age-associated decline in maximal heart rate and left ventricular contractility during vigorous exercise probably reflects diminished β-adrenergic modulation of contractility, chronotropy and vasomotor tone with advancing age. β-

Table 9 Cardiorespiratory responses to exhaustive upright exercise; LV=left ventricular, SVR=systemic vascular resistance (adapted from references 28 and 61)

	Peak response at 20 yr	**Change in peak response between 20 and 80 yr**
LV end-diastolic volume	no change, or decrease	increase (c.30%) in males, no change in females
LV end-systolic volume	decrease	decrease (c.100%)
Ejection fraction	increase	decrease (c.15%)
Stroke volume	increase	no change
Heart rate	increase	decrease (c.25%)
Cardiac output	increase	decrease (c 25%)
Stroke work	increase	increase (c.15%) in males, no change in females
SVR	decrease	increase (c.30%)
Systolic arterial pressure	increase	no change in males, increase (c.10%) in females
Oxygen consumption	increase	decrease (c.50%)
Plasma catecholamines	increase	increase
Myocardial contractility	increase	decrease (c.60%)
β-Adrenergic modulation	fully functional	decrease

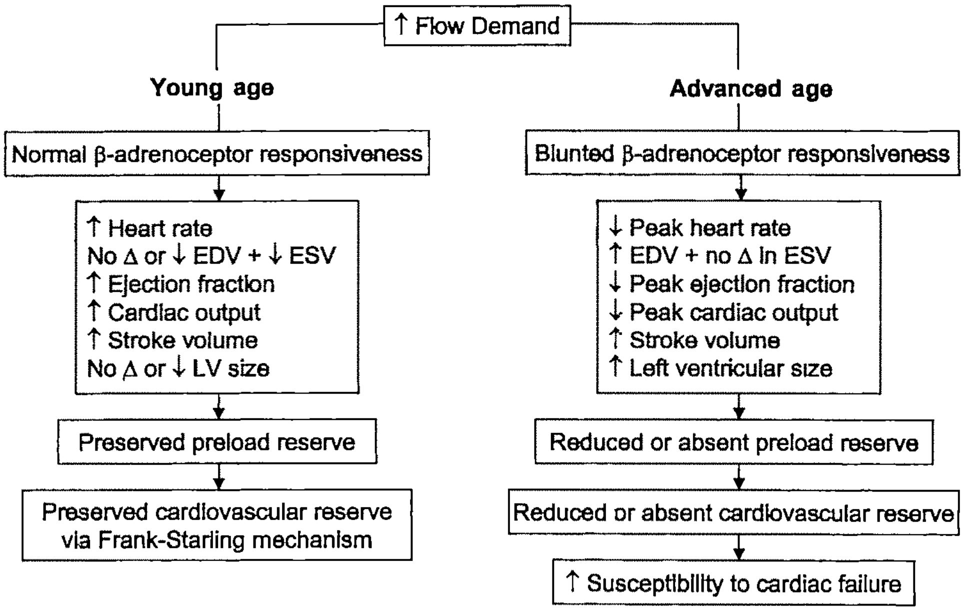
↑ Flow Demand
Young age
Advanced age
Normal β-adrenoceptor responsiveness
Blunted β-adrenoceptor responsiveness
↑ Heart rate
No Δ or ↓ EDV + ↓ ESV
↑ Ejection fraction
↑ Cardiac output
↑ Stroke volume
No Δ or ↓ LV size
↓ Peak heart rate
↑ EDV + no Δ in ESV
↓ Peak ejection fraction
↓ Peak cardiac output
↑ Stroke volume
↑ Left ventricular size
Preserved preload reserve
Reduced or absent preload reserve
Preserved cardiovascular reserve via Frank-Starling mechanism
Reduced or absent cardiovascular reserve
↑ Susceptibility to cardiac failure

Fig 2 Cardiac response to increased flow demand in the young and the elderly. The young meet the increased flow demand primarily by β-adrenoceptor-mediated augmentation of heart rate and contractility, thus preserving preload reserve via the Frank–Starling mechanism. In contrast, the elderly employ primarily the preload reserve to augment cardiac performance, thereby losing additional cardiovascular reserve and becoming susceptible to cardiac insufficiency. EDV=end-diastolic volume; LV=left ventricular; Δ=change.

Adrenoceptor blockade effectively converts the haemodynamic profile of young men to that more typical of older men across submaximal work rates.[29] This finding supports the hypothesis that blunted β-adrenoceptor responsiveness underlies the attenuated increases in heart rate and myocardial contractility, and the cardiac dilation that occur during exhaustive exercise in older individuals.

The clinical implications of blunted β-adrenoceptor responsiveness with advancing age are considerable. The young respond to increased flow demands primarily with sympathoadrenergic activation, followed by β-adrenoceptor-mediated modulation of cardiovascular performance (Fig. 2). Such a mechanism maintains heart size despite increases in heart rate, venous return and systolic arterial pressure. As preload reserve is preserved, additional flow demands can be met by activation of the Frank–Starling mechanism, i.e. by increasing end-diastolic volume.

In contrast, in the elderly, the increased peripheral flow demand is met primarily by activation of the preload reserve (Fig. 2). As no further compensatory mechanism exists, additional flow demands may result in cardiovascular insufficiency. Such reduced cardiovascular reserve capacity explains the higher incidence of acute and chronic heart failure in the elderly. The cardiovascular response to exercise in the elderly is comparable to disease states such as congestive heart failure. It emphasizes the importance of peripheral vasodilation.

The clinically most relevant alterations in cardiovascular physiology with ageing are increased myocardial and vascular stiffness, blunted β-adrenoceptor-mediated modulation of inotropy, chronotropy and vasomotor tone, and autonomic reflex dysfunction. The increase in myocardial stiffness decreases left ventricular compliance which, in turn, impairs diastolic function. These changes are reflected by reduced early diastolic filling rate, elevated end-diastolic volume in elderly men and a tendency for higher cardiac filling pressures. Despite maintained stroke volume and ejection fraction, the increase in end-systolic volume in elderly men reflects an age-dependent decline in intrinsic myocardial contractility.

Although the cardiac adaptation to arterial stiffening will help to maintain systolic function and myocardial oxygen supply/demand balance, diastolic function will be impaired even further. In general, however, despite evidence of impaired diastolic and systolic function in elderly males, overall cardiac performance is adequately maintained at rest during advancing age. Despite arterial stiffening, pump function is maintained via various adaptations which include a moderate increase in left ventricular wall thickness, prolonged contraction, atrial enlargement, enhanced atrial contribution to left ventricular filling and elevated end-diastolic volume in males. The age-related alteration in cardiaovascular response to a change in posture or exercise is probably caused more by autonomic reflex dysfunction and blunted β-adrenoceptor responsiveness with advancing age than by impaired myocardial function.

Age and cardiovascular disease

Ageing affects cardiovascular risk factors, incidence and clinical manifestation of cardiac disease, treatment strategies and prognosis.[60] Cardiovascular disease is superimposed on age-associated changes in cardiac and vascular characteristics. The final pathophysiological mechanism and clinical presentation result from an interaction between age-related changes in cardiovascular physiology and cardiovascular disease.

Chronic ischaemic heart disease

The diagnosis of ischaemic heart disease may be more difficult in the elderly. Reduced physical activity with age limits the occurrence of demand angina. Possibly related to the age-related changes in myocardial compliance and diastolic relaxation, dyspnoea, rather than pain, may dominate the clinical picture of myocardial ischaemia and infarction. The predictive value of a negative exercise stress test is low in a population with a high prevalence of ischaemic heart disease. As many elderly people are unable to exercise to 85–90% of their predicted maximum heart rate, a pharmacological stress test with thallium scan or echocardiogram is often of greater diagnostic accuracy.[60]

Although the goal and choice of anti-ischaemic treatment are generally similar in young and old patients, the elderly must be expected to be more sensitive to the hypotensive effects of certain anti-ischaemic drugs because of blunted baroreceptor reflex activity and sympathetic responsiveness, and increased myocardial and vascular stiffness. As a result of the same age-related decrease in sympathetic responsiveness, myocardial ischaemia is less likely to be provoked by adrenergic-mediated increases in myocardial oxygen demand and the benefit derived from treatment with β-adrenoceptor blockers may be reduced.

Acute myocardial infarction

In the elderly, in-hospital and subsequent mortality, reinfarction and complications are all increased.[4,60] Likewise, perioperative myocardial infarction carries a considerably higher mortality in the elderly.[19,20,39] In addition, age is an independent predictor of adverse outcome following various therapeutic interventions, such as percutaneous transluminal angioplasty (PTCA), coronary stenting and thrombolysis.[1,6,47,101,108]

Increased mortality and morbidity in the elderly after myocardial infarction and therapeutic cardiovascular interventions have many causes. They include greater impairment of baseline left ventricular function, more advanced multivessel disease, higher rate of major complications,[1] greater risk of cardiac rupture despite comparable infarct size (probably on the basis of age-related morphological changes), higher rate of vascular complications,[1] increased incidence of non-cardiac complications (e.g. stroke and haemorrhage), greater likelihood of interventions being performed under emergency conditions,[1] lower procedural success,[1] more contraindications to thrombolytic therapy, longer times between onset of symptoms and presentation for evaluation and treatment, blunted catecholamine response, impaired renal and respiratory reserve, and coexisting diseases.[1,60,81]

Congestive heart failure

Determination of whether there is predominantly a systolic or a diastolic component to heart failure is particularly important in the elderly because approximately 40% of patients aged >60 yr with symptoms of congestive heart failure have preserved systolic function. The treatments for systolic and diastolic dysfunction are different, and older people are less able to compensate for adverse cardiovascular drug effects.

Arrhythmias

Arrhythmias occur more frequently and are more often associated with haemodynamic compromise in older people. Atrial fibrillation is the most common supraventricular arrhythmia in individuals aged >65 yr. It often impairs cardiac performance because ageing people become progressively dependent on atrial contribution to diastolic filling. Any compromise in cardiac output or arterial

Table 10 Possible relationships between age-related cardiovascular changes and clinical impairment; LV=left ventricular; LA=left atrial (modified from reference 61)

Cardiovascular change	Pathophysiology	Clinical impairment
1. Cardiac		
increased myocardial stiffness	decreased LV compliance	lower threshold for dyspnoea
altered conduction system morphology	irregular conduction	greater prevalence of arrhythmias
increased LA size	increased LA pressure/ distension	greater prevalence of lone atrial fibrillation
2. Vascular		
increased vascular stiffness	increased aortic impedance	systolic hypertension, LV hypertrophy
3. Cardiovascular		
increased myocardial stiffness + increased vascular stiffness	decreased cardiovascular reserve	decrease in exercise tolerance lower threshold for, and greater severity of heart failure
+ autonomic dysfunction + decreased β-adrenoceptor responsiveness	decreased baroreceptor reflex activity	greater susceptibility to postural hypotension and syncope

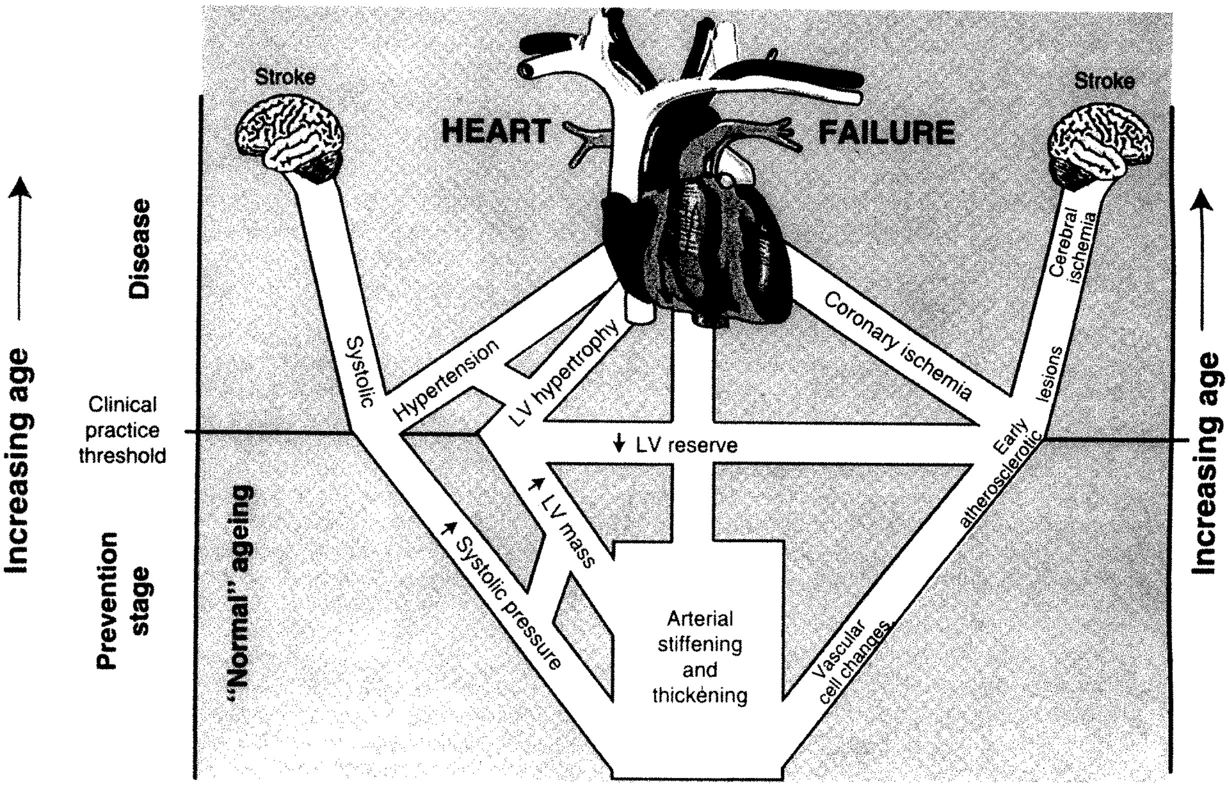

Fig 3 Changes in vasculature and heart with ageing, leading to cardiovascular disease with advancing age. The line bisecting the top and bottom parts indicates the point when 'normal' ageing (below the line) will produce symptoms of disease (above the line). (Reproduced with permission from Lakatta EG. Aging effects on the vasculature in health. Risk factors for cardiovascular disease. *Am J Geriatr Cardiol* 1994; **3**: 11–17.)

pressure may lead to a critical decrease in cerebral perfusion in the elderly because of blunted β-adrenoceptor responsiveness, increased vascular stiffness and a greater likelihood of pre-existing cerebrovascular disease. The higher prevalence of atrial fibrillation in older people results from the age-related increase in left atrial size and workload, and an age-associated higher incidence of atrial fibrillation-inducing electrolyte imbalances, digoxin overdose, clinical or subclinical hyperthyroidism, anaemia and congestive heart failure.

Although the diagnostic and therapeutic principles of managing cardiac disease are comparable in older and younger patients, accompanying diseases, changes in life-style habits and altered pharmacokinetics and pharmacodynamics (see below) render overall management more difficult in older patients. Relevant data are lacking, so an evidence-based approach to cardiovascular care in the elderly is difficult.[82]

It is to be expected that age-related cardiovascular changes are associated with cardiovascular diseases (Table

Table 11 Age-related changes in non-cardiovascular organ function

Respiratory	increased chest wall rigidity, increased work of breathing, decreased respiratory muscle strength and endurance (*c* 20% decrease by 70 yr), decreased functional alveolar surface area (*c* 15% decrease by 70 yr), decreased response to hypoxaemia and hypercapnia, decreased vital capacity (*c*.20–40 ml yr^{-1}), increased residual volume (*c* 30% of total lung capacity at 70 yr), increased closing volume, decreased gas exchange (*c* 0.5% yr^{-1})
Renal	reduction in number of nephrons (*c* 0.5–1.0% yr^{-1}, mostly cortical), reduced glomerular filtration rate (*c* 30–50% decrease by 70 yr), decrease in renal blood flow, decrease in urine-concentrating ability, reduction in ability to conserve sodium, decreased tubular secretion, reduction in total body water (*c* 10–15% decrease by 80 yr), lower thirst perception
Hepatic	reduction in hepatic mass (*c*.40% decrease by 80 yr), reduction in hepatic and splanchnic flows (*c* 40% decrease by 80 yr), decrease in activity of microsomal demethylation pathway, decrease in activity of hepatic cholinesterase
Miscellaneous	reduction in skeletal mass, lower metabolic requirement (*c* 10–15% lower by 80 yr), reduced body heat production, decrease in thermoregulatory vasoconstriction, reduction in number of neurons (*c* 15% decrease by 80 yr), reduced adrenal mass (*c*.15% decrease by 80 yr), reduced cortisol secretion (*c* 15% decrease by 80 yr)

10). Figure 3 illustrates the continuum between the 'normal' ageing process (below the line bisecting top and bottom parts) and clinically perceived disease (above the line).[59] At some point, 'normal' ageing will produce signs and symptoms that we usually equate with disease. In old age, the pathophysiology of age-independent cardiovascular disease is superimposed on the age-related alterations in cardiovascular structure and function. Such an interaction may change the typical clinical presentation of a given disease in a way that delays diagnosis and treatment, and thereby even worsens long-term outcome. There will obviously be a time when the patient will have relevant cardiovascular alterations that are not apparent at rest, but which become clinically relevant at times of increased cardiovascular stress.

Age-related changes in non-cardiac organ function

Respiration

Age-related changes in structure and function of the respiratory system have been well described (Table 11).[13] The clinical implications are multiple and may well affect cardiovascular risk in the elderly.

The increased baseline work of breathing limits the capacity to meet additional workloads postoperatively and renders the elderly prone to the development of acute postoperative respiratory failure. Older patients are more likely to develop apnoea, periodic breathing and respiratory depression after the administration of opioids and benzodiazepines. Their compensatory physiological response to hypoxaemia and hypercapnia is smaller and delayed. This and lower baseline arterial oxygen tension (Pa_{O_2}) increase the risk of perioperative hypoxaemia, which may contribute to myocardial ischaemia and infarction, particularly in patients at increased cardiac risk.

Kidney

As the kidney plays a critical role in fluid and electrolyte balance, an age-related decline in renal function (Table 11)[66] may contribute to increased cardiovascular risk in the elderly. In the presence of impaired cardiovascular compensatory mechanisms, delayed excretion as well as conservation of free water and salt render the aged patient prone to hyper- and hypovolaemia, hypertension and hypotension, and heart failure.

The age-related decreases in thirst, renin response and urine-concentrating ability[96] facilitate sodium and volume depletion. Any sodium depletion may impair the Starling mechanism on which the elderly depend to maintain cardiac output and arterial pressure during various forms of cardiovascular challenge. Concurrent diseases also associated with sodium and volume loss (e.g. diarrhoea, vomiting, short-term renal losses) may further unmask the limited adaptive cardiovascular capacity in the elderly. All of this may predispose the elderly to syncope. Attention to fluid and electrolyte balance is particularly important in the elderly.

It is conceivable that the insufficient cardiovascular response to postural changes serves as a non-osmotic stimulus for the release of vasopressin, possibly resulting in hyponatraemia. This electrolyte imbalance is not uncommon in the elderly during disease, treatment with diuretics, or in the perioperative period.

Liver

Age-related hepatic changes (Table 11)[50,110] may impair the functional hepatic reserve to meet the increased demands of metabolism, biotransformation and protein synthesis after surgery and its complications.

Thermoregulation

Advancing age predisposes a patient to perioperative hypothermia.[33,57,103] Contributing factors include frail constitution, reduced metabolic rate, reduced subcutaneous fat layer, major and long operations, and impaired thermoregulation.[104]

Adverse effects of perioperative hypothermia include prolonged drug action,[45] negative postoperative nitrogen balance,[12] impaired coagulation,[102] immune dysfunction and subsequent increased incidence of wound infection,[58] leftward shift of the haemoglobin–oxygen saturation curve,

Table 12 Age-related changes in drug disposition (adapted from reference 72)

Altered drug distribution	decreased total body water, decreased lean body mass, increased body fat, decreased serum albumin, increased α_1-acid glycoprotein
Altered hepatic metabolism	decreased hepatic mass, decreased hepatic blood flow, reduced activity of microsomal oxidizing system, reduction in presystemic metabolism of drugs with high rate of hepatic extraction
Altered renal excretion	reduced glomerular filtration rate, decreased concentrating ability, decreased renal blood flow

increased vascular resistance, cardiac arrhythmia, and up to four-fold increases in cardiac output and VO_2 associated with rewarming and shivering. Several of these factors impose a high load on the cardiovascular system. Not surprisingly, even in the absence of shivering, mild intraoperative hypothermia can be associated with an increased incidence of postoperative myocardial ischaemia and angina in older patients.[32]

As part of the 'normal' ageing process, most organ systems lose approximately 1% of their function per year, beginning at around 30 yr. However, there is considerable individual variability in decline. The hallmark of ageing is not necessarily a decline in resting levels of performance, but a lack of functional reserve and inability of organ systems to respond to external stress. Ageing organ systems may not have the functional reserve to meet increased perioperative oxygen demands, and may thus contribute to perioperative cardiovascular morbidity.

Drug therapy

The incidence of adverse drug reactions is two to three times higher in the elderly;[72] this is probably related to the reduced physiological reserve of most organ systems with advancing age, greater severity of disease to be treated, coexisting diseases, altered pharmacokinetics and pharmacodynamics, polypharmacy and intake of drugs with low therapeutic index (e.g. digoxin, antiarrhythmics).

Pharmacokinetics are largely dependent on drug distribution, hepatic metabolism and renal excretion. All of these change with advancing age in an unpredictable manner (Table 12). Drug distribution is affected by age-related decreases in total body water and lean body mass, relative increase in body fat, decrease in serum albumin, increase in α_1-acid glycoprotein, decrease in cardiac output and reduction in blood volume. Drugs that are usually highly protein bound (e.g. lidocaine, propranolol, thiopental, etomidate, propofol, alfentanil and fentanyl) may have an exaggerated clinical effect because a greater proportion of the drug is free (unbound). The decreased distribution volume of water-soluble drugs (e.g. digoxin) may result in adverse reactions because of increased initial plasma concentrations. The increased distribution volume of fat-soluble drugs (e.g. thiopental, diazepam and midazolam) prolongs drug action. Injection of drugs into a contracted blood volume will produce higher initial plasma concentrations.

The effect of age on drug metabolism and excretion is related to changes in hepatic and renal function. Decreases in hepatic mass, hepatic blood flow, activity of the microsomal demethylation pathway, and presystemic metabolism of drugs with a high rate of hepatic extraction, will result in greater bioavailability of drugs with high intrinsic hepatic clearance, where the rate-limiting step in metabolism is hepatic blood flow (e.g. lipid-soluble β-adrenoceptor blockers, antiarrhythmics, most major tranquillizers and tricyclic antidepressants).[60 72] Age-related decreases in renal blood flow, glomerular filtration rate, tubular secretion and urine-concentrating ability contribute to reduced clearance of quinidine, digoxin and atenolol, diminished diuretic response to furosemide, and volume depletion.[60]

Advancing age alters pharmacodynamics. This may render the elderly more sensitive to a given concentration of drug. However, whereas the sensitivity to sedatives, inhalational anaesthetics and anticoagulants increases with advancing age, the responsiveness to β-adrenoceptor agonists and antagonists, and to digoxin decreases.[60 72] Nevertheless, the therapeutic window for digitalis is narrower in older people because of a decreased inotropic effect without a change in arrhythmogenic potential. Use of non-steroidal anti-inflammatory drugs is associated with a higher incidence of hyperkalaemia, renal failure and death from gastrointestinal bleeding.

Underlying age-related changes in cardiovascular function and compensatory mechanisms, and increased prevalence of coexisting diseases render older patients more sensitive to the side-effects of cardiovascular drugs. Pre-existing volume contraction and decreased baroreceptor reflex function contribute to greater hypotensive and/or bradycardic responses to calcium channel blockers, nitrates and diuretics. Preexisting conduction system disease or left ventricular dysfunction increase the likelihood of side-effects following treatment with β-adrenoceptor blockers and certain calcium channel blockers.[60] Advanced age predisposes to clinically relevant volume depletion, hypokalaemia, hyponatraemia and hypomagnesaemia after diuretic therapy. As a result of marked heterogeneity of drug response in the elderly, no strict age-related rules can be applied across the entire geriatric population.

Anaesthetic implications

As with a young patient, perioperative anaesthetic management of an aged patient will be determined primarily by the patient's state of health, the anticipated surgical procedure and the skill and experience of the anaesthetist. Nevertheless, as the aged patient is not simply a chronologically older young individual, 'age adjustments' are often indicated, and sometimes essential.

Preoperative assessment

As the likelihood of adverse perioperative events increases with advancing age, preoperative assessment of organ function reserve becomes particularly important in the elderly. If there is evidence of cardiac impairment, quantification of such impairment is critical because the clinical presentation of the cardiac disease may be very atypical and may lead to a wrong diagnosis.

Preoperative risk stratification is particularly important in the elderly patient because often even the short- and intermediate-term prognosis is limited. It makes very little sense to subject an aged patient with severely reduced organ function to a major operation, knowing that the perioperative morbidity and mortality are prohibitively high. Effective preoperative risk stratification may modify preoperative therapy, surgical approach, choice of anaesthetic technique and agents, perioperative monitoring and postoperative care.

When major predictors (Table 1) are present, surgery is usually cancelled or delayed until the cardiac problem has been diagnosed and appropriately treated.[43] In the presence of intermediate predictors, further management depends on the patient's functional capacity (Table 2) and the surgery-specific risk (Table 3). Poor functional capacity or a high-risk surgical procedure justify preoperative cardiac assessment by additional non-invasive testing (e.g. exercise stress testing, pharmacological stress testing such as dipyridamole-thallium myocardial perfusion imaging or dobutamine stress echocardiography). The need for additional coronary angiography will depend on the results of the non-invasive testing. Subsequent care (e.g. cancellation or delay of surgery, revascularization, intensified medical management) is dictated by the findings of non-invasive testing and coronary angiography, and by the response to treatment.

Although minor predictors *per se* have not been proven to predict negative perioperative cardiac outcome independently, additional preoperative non-invasive cardiac testing and possibly (depending on the results) coronary angiography may, when combined with a high-risk surgical procedure, be justified. Such a consideration also applies to advanced age.

The number of clinical markers, degree of functional capacity and extent of surgery-specific risk will influence preoperative management (e.g. adjustment or initiation of medical therapy, need for additional non-invasive or invasive cardiac testing), perioperative cardiac monitoring (e.g. right-heart catheterization, transoesophageal echocardiography, real-time ST-segment monitoring) and postoperative care (e.g. admission to an intensive care unit, intense pain control, continuation or initiation of cardiovascular medication). Such modification of perioperative management should improve the short-term and long-term perioperative cardiovascular outcome.

The identification of candidates for possible preoperative coronary revascularization (by PTCA, stenting or bypass grafting) is difficult and remains a topic of considerable controversy. In general, the indication for coronary revascularization in the perioperative setting should be identical to that in the medical setting.[43] If it is confirmed that aggressive perioperative therapy with β-adrenoceptor blockers is effective in successfully reducing perioperative cardiac morbidity and mortality in cardiac high-risk patients,[83] the role of preoperative coronary angiography and revascularization may greatly diminish.[65]

Anaesthetic management

Older patients often come to the operating room with depleted volume because of overly conservative nil-by-mouth orders, reduced thirst, age-related decline in renal capacity to conserve water and salt, disease-associated fluid and electrolyte losses, inadequate intravenous fluid substitution and more frequent use of diuretics. Intravascular volume sensitivity has been repeatedly demonstrated in the elderly.[97] Older individuals made hypovolaemic by diuretics and salt restriction exhibit a greater decline in arterial pressure in response to upright tilting than both young hypovolaemic or old normovolaemic subjects.[97]

Likewise, because of decreased left ventricular compliance and limited β-adrenoceptor responsiveness, the elderly, particularly those with hypertension, must be expected to be more sensitive to fluid overload. Careful volume assessment before induction of anaesthesia is, therefore, even more important in the elderly than in the young, especially when major fluid shifts are anticipated.

Anaesthesia itself,[11] and all intravenous and volatile anaesthetics,[9 80 86 87 89] interfere with cardiovascular performance in one way or another. Induction of sleep withdraws sympathetic nerve activity[11] on which the aged with impaired cardiac performance may depend to maintain adequate perfusion pressure. In addition to this indirect effect, all anaesthetic drugs interfere with cardiovascular performance, either by direct effects on the heart and vasculature, or indirectly by modifying the neurohumoral control mechanisms of the circulation.[21 86 87] The direct effects include negative inotropy, impairment of diastolic function, and arterial and venous vasodilation. The indirect effects include decrease in central sympathetic outflow,[22 24 95] interference with vagal control of heart rate,[36 48 99] vagal stimulation[9] and depression of baroreceptor reflex control.[21 22 24]

For these reasons, more frequent and severe hypotension on induction of anaesthesia must be anticipated in the elderly because the direct and indirect effects of the anaesthetics occur on top of age-related impaired cardiovascular compensatory mechanisms. In this regard, the haemodynamic stability after administration of etomidate in patients with heart disease is remarkable.[40] Preserved sympathetic nerve activity and autonomic reflexes may contribute to this stability.[24] Etomidate may, therefore, be the induction agent of choice in aged patients with limited cardiovascular reserve.

The dose requirement of many hypnotic and analgesic drugs used in anaesthesia is reduced in elderly patients as a result of age-related changes in pharmacokinetics,[100] pharmacodynamics[38 49 51 74 91] or both.[52 70 91] In old age, anaesthetics may exert quantitatively as well as qualitatively different cardiovascular effects. For example, isoflurane becomes more cardiodepressant than halothane with advancing age.[69] The cardiovascular depression caused by propofol can be rather pronounced in the elderly.[7 54] Therefore, more judicious use and selection of agents, and slow titration of reduced doses during induction and maintenance of anaesthesia, are required with advancing age.

The incidence and severity of adverse drug interactions between anaesthetic and chronically administered cardiovascular drugs are likely to be greater in the elderly because of diminished cardiovascular reserve, more frequent use of cardiovascular medication (often with a narrow therapeutic window) and altered pharmacokinetics and pharmacodynamics. If the choice and dose of anaesthetic are not adjusted accordingly, arterial pressure and heart rate can decline considerably, and bradyarrhythmias may develop in patients aggressively treated with β-adrenoceptor blockers, calcium channel blockers, inhibitors of angiotensin-converting enzyme, and angiotensin receptor antagonists.

Transition from spontaneous to controlled ventilation will acutely reduce venous return and, subsequently, cardiac filling in patients who rely more heavily on adequate preload than the young. Hyperventilation must therefore be avoided in the elderly. Whenever practical, maintenance of spontaneous respiration is preferred to controlled ventilation in the aged cardiovascular risk patient. The combination of generous use of induction agents and aggressive ventilation may result in disastrous hypotension in the elderly.

Monitoring

As cardiac performance in the elderly becomes progressively dependent on preload conditions, the margin of safety declines with advancing age. As a result of age-related myocardial and vascular stiffness, reduced β-adrenoceptor responsiveness and autonomic dysfunction, inappropriately low preload will lead to a marked fall in cardiac output and arterial pressure (and, thus, in perfusion of vital organs), whereas inappropriately high preload can quickly provoke signs and symptoms of left ventricular insufficiency (e.g. impaired oxygenation, alveolar oedema or dyspnoea). More liberal use of monitoring devices that permit determination of various indices of preload and afterload (i.e. pulmonary artery catheter, transoesophageal echocardiography) may therefore be indicated in the elderly. This is particularly true for old patients with limited exercise tolerance who undergo a surgical procedure that is expected to cause considerable cardiovascular stress.[84 85]

Anti-ischaemic prophylaxis

Maintenance of, or initiation of, β-adrenoceptor blocker therapy in the perioperative period with the aim of maintaining heart rate at <80 beats min^{-1} must now be considered standard practice in the perioperative management of the aged patient at increased risk for, or having, ischaemic heart disease.[65 67 83 105]

Summary

It is mostly acknowledged that 'normal' or 'healthy' ageing of the cardiovascular system is distinct from the increasing incidence and severity of cardiovascular disease with advancing age (e.g. hypertension, ischaemic heart disease and congestive heart failure). It is also recognized that chronological and biological age may differ considerably. Nevertheless, even in the absence of overt coexisting disease, advanced age is always accompanied by a general decline in organ function, and specifically by alterations in structure and function of the heart and vasculature that will ultimately affect cardiovascular performance. Actual biological age is thus the net result of the interaction between age-related and concomitant disease-associated changes in organ function. As cardiovascular performance at a given moment is the net result of interactions between heart rate, intrinsic contractility, diastolic and systolic function, ventricular afterload and coronary perfusion, it is important to be aware of the age-related changes in each of these variables, independent of disease, as they determine cardiac performance at rest and its response to stress in the elderly.

The most relevant age-related changes in cardiovascular performance for perioperative management are the stiffened myocardium and vasculature, blunted β-adrenoceptor responsiveness and impaired autonomic reflex control of heart rate. These changes are of little clinical relevance at rest, but may have considerable consequences during superimposed cardiovascular stress. Such stress can take the form of increased flow demand (as in exercise or postoperatively), demand for acute autonomic reflex control (as in change of posture) or severe disease (as during myocardial ischaemia, tachyarrhythmias or uncontrolled hypertension). It may interfere with diastolic relaxation (i.e. ventricular filling), systolic contraction (i.e. ventricular emptying) and vasomotor control (i.e. arterial pressure homeostasis).

Three factors contribute most to the increased perioperative risk related to advanced age. First, physiological ageing is accompanied by a progressive decline in resting organ function. Consequently, the reserve capacity to compensate for impaired organ function, drug metabolism and added physiological demands is increasingly impaired. Functional disability will occur more quickly and take longer to be cured.

Second, ageing is associated with progressive manifestation of chronic disease which further limits baseline function and accelerates loss of functional reserve in the affected organ. Some of the age-related decline in organ function (e.g. impaired pulmonary gas exchange, diminished renal capacity to conserve and eliminate water and salt, or disturbed thermoregulation) will increase cardiovascular risk. The unpredictable interaction between age-related and disease-associated changes in organ functions, and the altered neurohumoral response to various forms of stress in the elderly may result in a rather atypical clinical presentation of a disease. This may, in turn, delay the correct diagnosis and appropriate treatment and, ultimately, worsen outcome.

Third, related to the increased intake of medications and altered pharmacokinetics and pharmacodynamics, the incidence of untoward reactions to medications, anaesthetic agents, and medical and surgical interventions increases with advancing age.

On the basis of various clinical studies and observations, it must be concluded that advanced age is an independent predictor of adverse perioperative cardiac outcome. It is to be expected that the aged cardiovascular risk patient carries an even higher perioperative cardiac risk than the younger cardiovascular risk patient. Although knowledge of the physiology of ageing should help reduce age-related complications, successful prophylaxis is hindered by the heterogeneity of age-related changes, unpredictable physiological and pharmacological interactions and diagnostic difficulties.

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SHORT COMMUNICATIONS

A Canadian simulation experience: faculty and student opinions of a performance evaluation study

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One hundred and forty-three students and 18 faculty at the University of Toronto participated in a study of the anaesthesia simulator as an evaluation tool. Both student and faculty opinions regarding the experience were elicited using questionnaires with a five-point scale, 1=strongly disagree, 5=strongly agree. Faculty and student opinion were similar and positive with respect to the use of the simulator and matching of educational objectives, its use as a learning experience, its use as an evaluation tool and the need for familiarity with the tool before use as an assessment method. This study supports the use of the simulator as an evaluation tool based on faculty and student opinions provided that prior exposure to the environment is offered.

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At the University of Toronto, medical students spend 2 weeks during their final year of medical school in an anaesthesia rotation. Final clinical evaluation is based on faculty assessments of daily student performance in the operating room. A written examination at the end of a 6-week block, consisting of 10 short answer questions, comprises 60% of the final mark. Educational literature documents many studies attesting to the complexity of the evaluation of medical competence.[1–3] Undergraduate medical education has been fraught with arguments regarding the reliability and validity of assessments that are neither consistent nor standardized.[4] The introduction of the objective structured clinical examination (OSCE) by Harden in 1975 as an examination tool is now widespread in Canada and many other parts of the world.[5] However, due to the nature of the practice of anaesthesia, the use of the OSCE does not lend itself to comprehensive examination of anaesthesia skills and knowledge. The purchase and availability of the CAE-link simulator at the University of Toronto supplies the means whereby the standardized assessment of performance of undergraduates can be undertaken during their anaesthesia rotation. The validity and reliability of any new assessment tool is important and has been addressed in a previous pilot study.[6] Using the same methodology as the pilot project, a subsequent study involving all final year medical students was undertaken. As part of this study, it was deemed important to gather opinions from participants to see if they endorsed the use of this innovative technology for evaluation and educational purposes.

Methods and results

The Canadian Simulation Centre for Human Performance and Crisis Management Training, housed at Sunnybrook Health Sciences Centre, incorporates a full-sized simulated operating room with adjacent control and storage areas and two debriefing rooms. The computer mannequin, complete with a drug recognition system, responds in an appropriate manner to pharmacological and physiological interventions. The mannequin itself has the ability to emit vocal sounds from a distant operator, has breath and heart sounds, and eyelid movements. Technical skills such as manual ventilation of the lungs, tracheal intubation and chest tube

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Table 1 Student evaluation of a simulator evaluation experience (n=145). Scale: 1–5, 1=strongly disagree, 5=strongly agree

#	Item	Median	Range
1	The video introduction was helpful	4	2–5
2	I understand the purpose of this experience	4	1–5
3	I felt comfortable in the simulator setting	3	1–5
4	The simulator experience reflected a realistic operating room situation	4	1–5
5	The scenarios reflected the learning objectives	4	1–5
6	Feedback was given	4	1–5
7	I learned something from this experience	4	1–5
8	The simulator might be used as an evaluation tool for medical students	3	1–5
9	Prior simulator exposure is needed before its use as an evaluation tool	5	1–5

insertion can be performed. Emergency carts for difficult intubation and defibrillation are available for use when needed.

After ethics approval from the University of Toronto Research Ethics Board was obtained, all 177 final year medical students at the University of Toronto were invited to participate in this study during the 1998–1999 academic year. Eighteen faculty agreed to be either video evaluators or simulator facilitators. A workshop for faculty was held to review the purpose of the study and to ensure that protocols used for simulator sessions and evaluation were understood. Ten faculty were assigned as video viewers and eight as facilitators in the simulator.

Six scenarios were designed incorporating the learning objectives of the curriculum. Evaluation protocols for each scenario were developed with five sections: preoperative assessment, preparation, induction, and two intraoperative problems.

All students were given an information sheet regarding the purpose of the study. It was also made clear that their simulator performance evaluation would not be used towards their final grade nor would they receive a mark related to the session. If they agreed to participate, a consent form was signed. On a scheduled educational day during the second week of their 2-week rotation, students worked through a 15-min faculty-facilitated simulator scenario. These sessions were videotaped. Two faculty reviewed and evaluated each student's videotaped performance. At the end of the simulator sessions, students met with the attending faculty and group feedback was given, and the learning objectives were addressed in detail. After the feedback session was completed, students were asked to complete an evaluation form summarizing their impression of the experience. Students were asked to respond to nine items using a five-point Likert scale from 1 to 5, 1=strongly disagree, 5=strongly agree. Comments were solicited. Opinions regarding the specifics of the simulator experience, content of the scenarios, realism and value of the simulator as an educational and evaluation tool were addressed. Responses were anonymous.

At the completion of the study, faculty, including the study co-ordinator, were asked to provide feedback regarding the experience using a questionnaire and the same Likert scale (n=19). Responses to 15 items were solicited together with comments pertaining to the items. Comments on the audio-visual qualities, the educational content and the value of the simulator as an evaluation tool were requested. The final item addressed the willingness to participate in further simulator research.

There was a 100% return rate of student questionnaires (n=145). Not all students completed all items, medians and range reflect the number of students who completed the items.

Table 1 shows the median and range of students' responses. Students rated the simulator highly as a learning experience and felt strongly that prior exposure to the simulator was needed if it were to be used as an evaluation tool.

There was a 94% return rate of faculty questionnaires (n=18). Four identical items were given to both faculty and students. These items are as follows: (i) matching of simulator scenarios to curriculum learning objectives; (ii) the value of simulation as a learning experience; (iii) use of simulator as an evaluation tool; (iv) prior exposure to simulator before its use as an evaluation tool. The median of faculty opinions was identical to those of students for items (i) and (iii) with a median of 4 and 3, respectively. The response to item (i) supported the belief that scenarios represented the undergraduate curriculum objectives. The reservation of both faculty and students regarding the use of the simulator as an evaluation tool appeared to be related to the fact that the environment was foreign to most students. Faculty felt that prior exposure to the simulator setting less important than students did with a median response of 4 by faculty and 5 by students. Faculty felt more positive than students with respect to the use of the simulator as a learning experience, although both groups rated its use as a learning experience very highly (median: faculty 5, student 4). Videotapes provided an adequate view of students' performance (median 4, range 3–5), but the audio system was found to be less than adequate during a few scenarios (median 2, range 1–4). Faculty indicated a desire to continue their participation in future simulator research (median 4, range 1–5).

Comment

Students found the sessions to be an excellent learning experience and pages of comments to this effect were elicited. The response of participants to the use of the simulator as an evaluation tool was less enthusiastic than its use as a learning tool. Thirty-eight percent of students agreed or strongly agreed and the same percentage disagreed or strongly disagreed on the use of the simulator as an evaluation tool, with faculty opinions demonstrating a similar trend. Students and faculty who disagreed expressed the need for experience in a simulator setting before an evaluation process.

In order for this tool to be introduced as an evaluation method, participants' opinions should be addressed, and where appropriate, integrated into the proposed assessment technique. With respect to undergraduates and faculty at our institution, important opinions have been elicited that will strengthen the ultimate integration of this innovative tool into undergraduate evaluation.

Acknowledgements

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Anaesthetists' attitudes to monitoring instrument design options

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A survey into the attitudes of anaesthetists to features in monitoring instruments, particularly the design of alarms, visual warnings, alarm limits and the general instrument interface is reported. Questions in the survey had short introductions outlining a clinical scenario followed by items that proposed alternative design features that an instrument might have. Participants were asked to grade their responses to these alternatives on a scale of 1 (strongly disagree) to 5 (strongly agree). The results suggest that anaesthetists would welcome the use of more advanced technology in instrument design. They prefer context-specific messages and alarms. They reject overt control systems for delivering anaesthesia, except for use in exceptional circumstances. Generally, the preferences of anaesthetists are consistent with known principles of safe, ergonomic design.

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This communication reports the results of a nationwide survey into the attitudes of anaesthetists to features in monitoring instruments, particularly the design of alarms, visual warnings, alarm limits and the general instrument interface. We set out to answer three questions. First, what sorts of design features are preferred by anaesthetists? Secondly, are these preferences consistent with the principles of safe, ergonomic design? Thirdly, do attitudes indicate ways to improve instrument design?

Methods and results

Survey design

The survey had three sections and was based on a previously validated questionnaire.[1 2] The first section consisted of a series of questions about the features of monitoring instruments. The questions were usually prefaced by a short clinical scenario. Responses were then invited to proposed alternative instrument design features relevant to the scenario. Participants were asked to grade their responses to each of these items on a scale of 1 (strongly disagree) to 5 (strongly agree). The wording of the questions and the items is shown in Table 1.

The second section requested details of the respondent and self-assessment on a five-point scale of computer literacy, computer access, general computer use and the use of computers in the operating theatre. The final section allowed free-form comments.

The questionnaire was sent to 1500 anaesthetists selected randomly from the British Medical Association membership list. Return was by Freepost through an enclosed pre-addressed envelope. Non-returners were followed up after 1 month with a new copy of the questionnaire and after 2 months by telephone to obtain information which was taken to be representative of non-responders.

Statistical analysis

Statistical analysis followed a standard form[3] using SPSS for Windows version 8.0. Responses were placed in order of popularity using the Friedman rank (highest, most popular). The mode was used to indicate the extent of agreement. After adjustment for item score skewness, exploratory factor analysis was performed using principal components analysis, which produces the most parsimonious description of factors. Used in this way, factor analysis seeks to find underlying groupings concordant with an identifiable underlying attitude.

Responses

In total, 504 valid replies were received, of which 382 were returned initially and 122 as a result of reminders. This return rate of 33.6% is disappointing but compares favourably with the best group in the preliminary study.[1 2] No significant differences between the background of responders and non-responders were demonstrated.

Question 1: how much control should a decision support system have?

The design options in the items for this question concerned the instrument having direct control of treatment and methods of presenting alarms and warnings. Three factors were identified. The first was about giving control of treatment to the machine, and was characterized by low ranks and modes for machine-centred approaches. The only acceptable situation identified as a candidate for machine control was when there were distinct signs of danger.

The second and third factors were about how warnings might be given. Public warnings (i.e. warnings that are visible/audible to other staff) characterized the second factor, whereas in the third factor the warnings were private. We conclude that anaesthetists see private warnings as serving functions different from public warnings.

Question 2: how should a computer decision support system communicate with the clinician?

In this scenario both warnings/alarms and advice were to be given by the instrument. The items contrasted flow diagrams and/or text with structured sounds[4 5] and spoken alarms. Advice was contrasted with warning in the items under this question. Three factors were identified: factor 1, all graphical; factor 2, all sounds; and factor 3, flow diagrams best used off-line. The anaesthetists showed a preference for thinking of audible systems only in terms of warnings. Audible advice had a low rank and mode.

Question 3: what is the best design of visual warnings on individual monitors?

In the situation of limited display space, idiographic symbols were contrasted with different text-based systems, and ranged from simple short messages to displays that had to be interpreted from an error code. Again, three factors were identified. The first concerned text-based options, in which the ranks, modes and factor weights were good. Factors 2 and 3 were non-homogeneous in design type. Idiographic designs appeared in both, mixed with text-based approaches.

Question 4: what is the optimal way of displaying alarm limits?

The final question concerned the design and positioning of alarm limit displays. Novel limit displays such as polygons[6] were included, along with more conventional colour-coded, numerical and graphical methods. Position options were also included. Two factors emerged from the analysis,

Table 1 Attitudes to monitoring instrument features Rank=mean Friedman rank for each item; mode = the mode of the item, weight = factor weightings using principal components analysis, the varimax rotation with Kaiser normalization. No factors with eigenvalues below 1.0 or items with a factor weight <0.41 are reported. Thus, all factors reported have equivalent statistical significances of $P<0.01$ Negative weights indicate that the scale of the item runs in the opposite direction to normal, i.e. the higher the respondent rating the lower the score on the scale

Items grouped by factors within questions	**Rank**	**Mode**	**Weight**
How much control should a decision support system have? *A computer decision support system connected to a machine (e.g a ventilator) being used to treat a patient detects a hazardous condition It should.*			
Under no circumstances change a patient's treatment automatically	7.72	4	−0.62
Change the patient's treatment if alarm is not cancelled and the vital signs show an unequivocally dangerous condition	6.75	4	0.93
Change the patient's treatment if alarm is not cancelled after given time	4.55	1	0.86
Change the patient's treatment without warning	2.30	1	0.92
Set off a non-specific audible alarm and put up a condition-specific visual alarm on a display	8.43	4	0.52
Set off a condition-specific audible alarm heard by other staff and patients	7.64	4	0.54
Set off a non-specific visual alarm and put up a condition-specific visual alarm	6.93	4	0.55
Set off a non-specific audible alarm heard by other staff and patients	5.28	2	0.78
Set off a non-specific visual alarm seen by other staff and patients	5.07	2	0.70
Set off a non-specific audible alarm only heard by staff treating the particular patient	6.65	3	0.73
Only put up a condition-specific message on the patient monitor but issue no general alarm	4.68	2	0.75
How should a computer decision support system communicate with the clinician? *Audible alarms and advice are to be given by the computer decision support system They should....*			
Offer extra physiological instrument displays	6.46	4	0.65
Offer graphical animated displays that suggest what is happening in the body but can be expanded into other displays on request	5.98	4	0.82
Include displays with more derived numerical information	5.52	3	0.70
Offer graphical animated displays that suggest what is happening in the body	5.41	3	0.80
Have audible alarms that are structured, i e bleeps, warbles, etc., indicating which measurement and intensity of alarm	6.44	4	0.46
Have alarms in words, e g *The blood pressure is too high*	5.29	4	0.70
Give instructions/advice about procedures as step-by-step text only	4.19	3	0.49
Not offer advice to the anaesthetist visually but by voice e.g *The carbon dioxide is rising so watch the placement of the laryngoscope*	2.25	1	0.75
Give instructions/advice about procedures as flow diagram boxes that can expanded into a full text explanation if required	7.69	4	0.84
Give instructions/advice about procedures as flow diagrams	5.78	4	0.84
What is the best design of visual warnings on individual monitors? *Many instruments used by anaesthetists are small with limited display space On such instruments visual warnings should*			
Combine an audible indication of urgency, e g a structure sound, with a grammatical message on the main display, e g *Oxygen low!*	7.22	4	0.67
Use short sentences of written text in English on the main display to describe the situation, e g. *Warning—the oxygen concentration is too low*	6.49	4	0.74
Combine a front panel-mounted indication of urgency, e.g a red light for most urgent warning) with a grammatical message on the main display, e g *Oxygen low!*	6.48	4	0.52
Use short grammatical messages, e g *Oxygen low!*, on the main display	6.33	4	0.70
Use idiographic symbols on the front panel of level of urgency, e g ⚠ = very urgent, combined with a grammatical message on the main display e g. *Oxygen low!*	6.00	4	0.53
Use idiographic symbols on the front panel, which are visible before they are activated and illuminated	4.02	3	0.83
Use annunciator style warnings with short text messages, where the warning is visible all the time but becomes illuminated when a warning occurs	3.77	3	0.73
Use numbers or letters for warning codes that have to be learned or looked up by the anaesthetist, e.g. *Error no 38 = temperature too high*	1.59	1	0.47
Use idiographic symbols presented on the main display, e g. 🔇 = alarms muted	7.47	4	−0.69
Combine an audible indication of urgency, e.g a structured sound, with an idiographic symbol on the main display, e g 🔇 = alarms muted	6.95	4	0.74
Use idiographic symbols on the front panel which are invisible before they are activated and back-lit	5.02	3	0.56
What is the optimal way of displaying alarm limits? *Research indicates that knowing what the alarm limits are whilst using anaesthetic equipment may be important in reducing the time it takes the anaesthetist to react to critical incidents Given the limitations of display space on most instruments, alarm limits should*			
Be colour-coded so they are linked with the waveform on the main waveform display	6.61	4	0.62
Be displayed permanently on the main graphical display of the instrument in relation to the measurement waveform	6.34	4	0.54
Be colour-coded for urgency	6.29	4	0.58
Be displayed numerically on the main waveform display	6.04	4	0.43
Be displayed graphically at the periphery of the waveform display	5.59	3	0.59
Be displayed graphically on the main waveform display	5.37	3	0.68
Be displayed on a specially designed display that integrates current values with the display limits, e.g. a polygon display or a riverbed display	5.08	3	0.59
Be displayed on demand on the main graphical display instrument in relation to the measurement waveform of the instrument	5.79	4	0.57
Be displayed numerically on a separate display away from the graphical display	4.45	2	0.68
Be displayed graphically on a separate display away from the graphical display	3.45	2	0.75

differentiated by whether the alarm limits are permanently visible near to the main display or further away. Close association of limits with the raw measurement data was preferred.

Comment

Bias

The biggest potential source of bias was that the responders were a self-selected group with a non-representative interest in instrument design. This sort of bias would explain the low return rate and is consistent with the tone of some of the comments made in the third section. We conclude that it is very hard, if not impossible, to avoid such self-selection. However, this may not be significant since these anaesthetists were most likely to have had an interest in equipment and were representative of those we most need to sample if improvements are to be made.

What sorts of design features are preferred by anaesthetists?

The results reported do not suggest that anaesthetists fear the use of more advanced technology in instrument design. In fact, many of the responses gave a cautious approval to more radical approaches than those incorporated in current instruments. Context-specific visual messages were preferred, as were sound-based designs with greater complexity, such as structured sounds. New measurements and more sophisticated displays were preferred, but detailed advice should be available off-line. Designs of visual warnings and alarm limits were considered immaterial provided they were easy to understand and closely associated with the main display of an instrument. The anaesthetists did not like systems that control the delivery of anaesthesia.

Are these preferences consistent with known principles of safe, ergonomic design?

Best practice in instrument design[7] emphasizes consistency, simplicity, redundancy and visibility as being good design principles. Most of the preferences of the anaesthetists were consistent with this approach. For example, the anaesthetists preferred condition-specific alarms in a hierarchy of alarms going from non-specific towards specific. However, offering more physiological measurements and more complex displays in an already overcrowded environment is not consistent with good ergonomics.

Can attitude research guide future safer designs?

The direct testing of instrument human factors performance in normal practice is virtually impossible because critical incidents are too rare. Therefore, testing requires simulation and measurements of performance which are surrogates of performance in the field (e.g. reaction time).[8 9] Some design features preferred by anaesthetists might be tested in this way. The results of such testing will demonstrate the validity of this attitude-based approach to detecting key features in design. If it is valid, the type of attitude survey reported here may prove useful in any environment.

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Effect of remifentanil compared with fentanyl on intraocular pressure after succinylcholine and tracheal intubation[†]

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Rapid sequence induction using succinylcholine is associated with an increase in intraocular pressure (IOP). This may lead to loss of ocular contents in open globe injuries. No method has previously been shown to prevent this increase in IOP. We investigated whether remifentanil, an ultra-short-acting opioid, could attenuate this increase in IOP during rapid sequence induction of anaesthesia. Forty-five patients were randomized blindly to receive remifentanil 1 μg kg^{-1}, fentanyl 2 μg kg^{-1} or placebo 1 min before thiopental, succinylcholine and tracheal intubation. IOP and haemodynamic variables were measured before, 1 min after the test solution, 30 s after thiopental, 30 s after succinylcholine, immediately after intubation and then every 3 min for 9 min. Remifentanil obtunded the increase in IOP after succinylcholine and intubation, so it could be suitable for use in open globe injuries.

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Rapid sequence induction is an established technique in emergency anaesthesia to minimize the risk of pulmonary aspiration. Succinylcholine is the neuromuscular blocking agent of choice in this clinical situation because of its short onset time. It is, however, associated with an increase in intraocular pressure (IOP). Laryngoscopy and tracheal intubation further aggravate the increase in IOP.

Remifentanil is an ultra-short-acting mu-receptor agonist. It has a rapid onset of analgesia, with a peak effect 1 min after administration.[1] Alexander, Hill and Lipham found that remifentanil 1 μg kg^{-1} given after induction with propofol 2 mg kg^{-1} prevented an increase in IOP after succinylcholine and tracheal intubation.[2] The effect of remifentanil with thiopental on IOP has not been described. This study was undertaken to determine if a bolus of remifentanil given before induction of anaesthesia with thiopental can obtund the IOP effects and haemodynamic changes associated with rapid sequence induction.

Methods and results

After obtaining Hospital Ethics Committee approval and informed consent, we studied 45 unpremedicated (ASA I or II) patients scheduled for elective surgery. Patients with ocular, respiratory or cardiovascular disease were excluded. The patients were randomized into three groups using sealed envelopes. Group R received remifentanil 1 μg kg^{-1}, group F received fentanyl 2 μg kg^{-1} and group P received normal saline as test solution. An applanation tonometer (Tonopen XL, Mentor O&O, Norwell, Massachusetts, USA) was used to measure the IOP in triplicate (mean value recorded) by one of the investigators (H.-P.N. or F.-G.C.) who was unaware of the test drug to be given.

Amethocaine 1% drops were instilled on the patient's left eye and baseline IOP was measured (time I). After 3 min of preoxygenation, a bolus of test solution diluted to 10 ml was administered over 30 s. Measurement was repeated 1 min later (time II) and anaesthesia was then induced with i.v. thiopental 5 mg kg^{-1}. At loss of eyelash reflex (time III), IOP was recorded and succinylcholine 2 mg kg^{-1} administered. Thirty seconds later (time IV), IOP was measured. Laryngoscopy and intubation were then performed and IOP was measured immediately and every 3 min for 9 min (times V–VIII). Anaesthesia was maintained with 1% isoflurane and 66% nitrous oxide in oxygen and ventilation adjusted to maintain normocarbia. At each IOP measurement, mean

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arterial pressure (MAP), heart rate, oxygen saturation, end-tidal PCO$_2$, peak airway pressure and inspiratory concentration of isoflurane were recorded. Intravenous atracurium was given after time VI to maintain muscle relaxation. Surgery only began after the study was complete.

Physical characteristics (except for gender, which was analysed using the χ^2 test), IOP, MAP and heart rate between groups were compared using one-way analysis of variance (ANOVA) with *post hoc* Bonferroni correction. Intra-group comparisons of IOP, MAP and heart rate differences from baseline were done using repeated measures ANOVA and *post hoc* Bonferroni correction. Results are expressed as mean (SD). A P value of <0.05 was considered significant.

There were no significant differences in physical characteristics (age, ASA status, gender or height) between groups except for weight between groups F and P (P=0.021). There were 10, 7 and 12 males in groups R, F and P, respectively. Mean (SD) ages were 31.8 (11.1), 35.5 (8.8) and 31.0 (10.1) yr; mean (SD) weights were 59.7 (11.1), 57.9 (7.6) and 69.1 (13.1) kg; and mean (SD) heights were 163.5 (7.0), 161.1 (7.4) and 169.0 (6.2) cm in groups R, F and P, respectively.

The values of heart rate, MAP and IOP are shown in Figure 1. No significant differences in heart rate among the three groups were recorded at any time. When comparing MAP between groups, significant differences were seen at times V–VII. The MAP of group R was significantly lower than that of group P at times V (P=0.018) and VI (P=0.004). Similarly, MAP in group F at times VI (P=0.024) and VII (P=0.006) was significantly lower than that in group P.

There were no significant differences in baseline IOP between the three groups. After giving the test solution, there was a significant decrease, compared with baseline, in IOP in group R (P=0.011) but not in group P or F. Thiopental decreased IOP significantly compared with baseline in all groups (point III in Figure 1) (P<0.001). Succinylcholine and intubation increased IOP in all groups. However, IOP in group R after intubation was not significantly different from that at baseline (point V in Figure 1), unlike that in the other groups (P<0.001 in group P; P=0.046 in group F).

There were significant differences in IOP between the three groups at times V–VII. The IOP of group R was lower than that of group P at times V (P=0.027), VI (P=0.02) and VII (P=0.015). When comparing differences from baseline IOP between the three groups, the difference in group R is lower than that at group P at times II and IV–VII and that of group F is significantly lower than that of group P at times V and VI (P<0.05).

Discussion

Succinylcholine is used during rapid sequence induction despite its effects on IOP because its speed of onset and effect allow intubation in 30–60 s. Its short half-life also allows fast recovery of muscle power if the airway conditions are difficult.

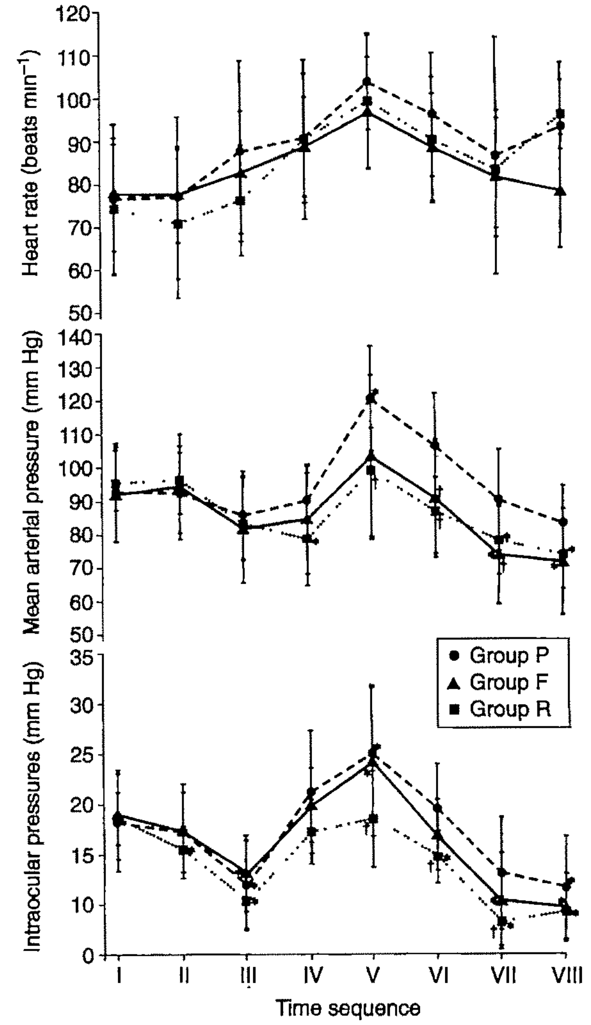

Fig 1 Multiple comparisons of HR, MAP, and IOP at times I to VIII. †P<0.05 compared with group P, *P<0.05 compared with baseline values within group (n=15 in each group). I=baseline, II=after test solution, III=after thiopental, IV=after suxamethonium, V=immediately after intubation, VI=3 min after intubation, VII=6 min after intubation, VIII=9 min after intubation.

Rocuronium, a new non-depolarizing neuromuscular blocking drug with a short onset time, has been found not to increase IOP.[3] Unfortunately, it does not provide as rapid and predictable intubating conditions as succinylcholine unless doses of three times the ED$_{95}$ are used.[4] Its long duration of action may then cause problems in the presence of an unexpectedly difficult airway.

In our study, fentanyl 2 μg kg^{-1} failed to attenuate the increase in IOP. Sweeney and colleagues found that fentanyl 2.5 μg kg^{-1} or alfentanil 10 μg kg^{-1} attenuated the increase in IOP associated with succinylcholine and intubation.[5] In their study, the larynx and tracheal were sprayed with lidocaine 1.5 mg kg^{-1} to reduce the deleterious effects of intubation. This is not usual practice in an emergency because attenuation of the gag reflex potentially increases the risk of aspiration. Our protocol attempts to simulate as closely as possible a rapid sequence induction technique.

Remifentanil is a new short-acting narcotic with a rapid termination of effect and a half-life of 8–10 min. It provides a profound, yet brief, period of analgesia of almost immediate onset. The main untoward effects of remifentanil are respiratory depression, bradycardia and muscle rigidity. We did not observe any of these effects despite giving the bolus of remifentanil over 30 s. There was also no complaint of nausea or difficulty in breathing.

In our study, remifentanil obtunded the increases in IOP associated with succinylcholine and intubation. This may be a result of the short onset time of remifentanil, producing a maximum decrease in IOP by the time of administration of succinylcholine and intubation. We administered succinylcholine at doses of 2 mg kg^{-1} and none of our patients coughed or gagged during intubation. In the study by Alexander and colleagues,[2] succinylcholine 1 mg kg^{-1} was used. Four patients either coughed or gagged and had to be excluded, possibly because of the low dose of succinylcholine used.

We chose thiopental as an induction agent instead of propofol, as it is more widely used for rapid sequence induction. Propofol decreases IOP more than thiopental, but causes significantly more hypotension.[6] Its combination with remifentanil may not be appropriate in elderly or hypovolaemic patients.

This study has limitations. The gold standard for measurement of IOP is the Goldman Tonometer, but this is impractical during rapid sequence induction of anaesthesia. The Tonopen XL is an electronic applanation tonometer which uses a micro strain gauge transducer. Previous studies had shown that IOP measurements made with the Tonopen were sufficiently close to those made with the Goldman tonometer and can be considered clinically accurate.[7]

The second limitation of this study was that it was conducted in patients with normal eyes rather than on patients with open globe injuries. The sequence of IOP changes in patients with open globe injuries may not be similar to those in patients with normal eyes. In an open globe, IOP is atmospheric and any increase in pressure results in further loss of ocular contents rather than an increase in IOP.

The third limitation of this study is that we used remifentanil at doses of 1 μg kg^{-1}; a dose of 2 μg kg^{-1} would be equipotent with the dose of fentanyl used (2 μg kg^{-1}). We were concerned about the side-effects of giving a bolus of remifentanil of >1 μg kg^{-1} over 30 s. The effect of remifentanil on IOP may be more pronounced had we given doses equipotent to that of fentanyl.

In conclusion, we found that remifentanil 1 μg kg^{-1} obtunded the increase in IOP associated with succinylcholine and tracheal intubation without any unwanted haemodynamic effects.

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CASE REPORTS

Non-invasive positive pressure ventilation for severe thoracic trauma

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A 35-year-old man was admitted to the intensive care unit (ICU) following a road traffic accident. He had sustained severe trauma to the left side of his chest, as well as other musculoskeletal injuries. After a short initial period of ventilation of the lungs via a tracheal tube, he was managed using a combination of continuous positive airway pressure and non-invasive positive pressure ventilation. He avoided ventilator-associated pneumonia, and spent a large part of his time on the ICU without any invasive monitoring lines, another potential focus of infection. He was discharged from the ICU after 25 days without having suffered any septic complications. The role of non-invasive positive pressure ventilation in severe thoracic trauma is discussed.

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Victims of thoracic trauma are often referred to critical care services for assistance with analgesia and ventilation. Some of these patients have historically required long periods of ventilatory support, and have therefore been at high risk of acquiring nosocomial pneumonia. We report a case in which a patient with severe thoracic trauma (Abbreviated Injury Scale score 5/6 for thoracic injury (where 0 represents no injury, and 6 represents an unsurvivable injury[1])) was managed mainly using non-invasive positive pressure ventilation (NIPPV), an approach which, we postulated, would be as effective as conventional ventilation, but expose him to a lower risk of nosocomial pneumonia.

Case report

A 35-year-old pedal cyclist was hit by, and trapped under, a heavy goods vehicle. He was extricated by the emergency services, and brought to the accident and emergency department on a spinal board. His Glasgow coma score was 15 throughout. He was complaining of severe left-sided chest pain and marked shortness of breath. He had a respiratory rate of 40 b.p.m., and the clinical features of a left flail chest. His oxygen saturation by pulse oximeter was 85% on a fractional inspired oxygen concentration ($F\text{I}_{O_2}$) of 0.6. This was thought to be accurate as the probe was on an uninjured limb, there was a good trace on the monitor, and the patient was centrally cyanosed. He was tachycardic, with a heart rate of 140 beats min^{-1}, and hypotensive, with an initial systolic blood pressure of 55 mm Hg. He was resuscitated initially with crystalloid solution, followed by blood when it was available. He received a total of 5.5 litres of crystalloid, followed by 9 units of packed red blood cells. His blood pressure responded well, if transiently, to intravascular filling.

A chest x-ray (Fig. 1) showed fractures of the second–ninth ribs on the left, with disruption of the costovertebral joints, resulting in a large flail segment. There was severe contusion of most of the left lung and contusion of the right lower lobe. He had a disruption of his left shoulder joint, a large laceration over his left iliac crest, and a fractured left ankle. His Revised Trauma Score was 6.0, which represents an expected mortality of approximately 10%, and his Trauma Score – Injury Severity Score (TRISS) expected mortality was 18%.[1]

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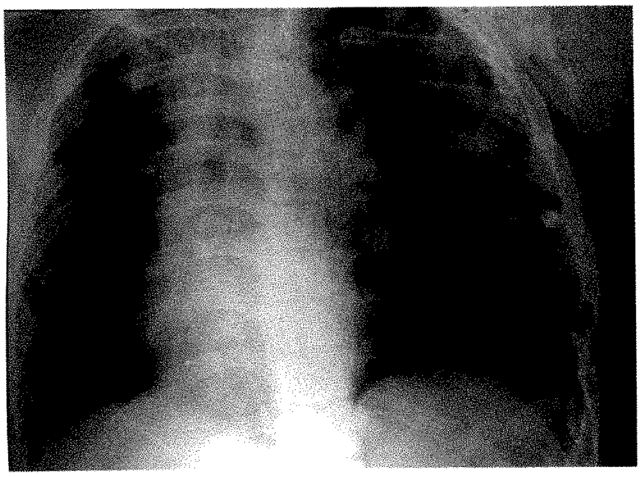

Fig 1 Admission chest x-ray, showing multiple left-sided rib fractures, massive left, and right lower lobe pulmonary contusion. A left intercostal drain is *in situ*.

In view of his injuries and cardiorespiratory instability, his trachea was intubated and his lungs ventilated. A left chest drain drained initially 500 ml of blood, but the loss quickly decreased. A right chest drain was inserted prophylactically, in accordance with current Advanced Trauma Life Support (ATLS) teaching for a patient with severe thoracic injury requiring positive pressure ventilation.[2] This approach has arisen in view of the high risk of an occult pneumothorax in such patients.[3 4]

Computed tomography (CT) of the chest, cervical and thoracic spine, performed after stabilization confirmed the initial chest x-ray findings, as well as revealing bilateral small pneumothoraces and fractures of many of the spinous processes of the thoracic vertebrae. The neural arches were, however, intact and there was no evidence of spinal cord injury. The cervical spine appeared normal.

The patient's lungs were ventilated using volume controlled ventilation, with a positive end-expiratory pressure (PEEP) of 6 cm H_2O, and an $F\text{I}_{O_2}$ of 0.35 (Servo 900C ventilator, Siemens-Elema, Sweden). This resulted in an arterial oxygen partial pressure (Pa_{O_2}) of 13.7 kPa. He was thought not to require an open lung strategy as his peak airway pressure was acceptable (<25 cm H_2O), and oxygenation was not problematic. His initial cardiovascular instability was such that high levels of PEEP were thought inadvisable.

After a 48-h period of stabilization, and once his coagulopathy (a result of the massive transfusion) had been treated by infusion of fresh frozen plasma and cryoprecipitate, a thoracic epidural was inserted at the T7/8 level, and infusion of bupivacaine commenced. The epidural provided good analgesia for the thoracic injuries, but the shoulder fracture continued to produce a lot of pain. A patient-controlled analgesia infusion of morphine was therefore also commenced. These infusions resulted in good analgesia, ventilatory support was weaned off, and his trachea was extubated on the fourth day after admission.

On day 5, increasing oxygen requirement was treated with periods of intermittent positive pressure breathing (IPPB) via a Bird ventilator and continuous positive airway pressure (CPAP) by facemask. IPPB is a form of treatment, usually administered by the physiotherapists, which is designed to reinflate collapsed pulmonary segments and so reduce shunting of deoxygenated blood. The patient uses a mouthpiece; the lungs are ventilated with a constant pressure. Despite this, by day 7 his $F\text{I}_{O_2}$ had risen to 0.6, giving a Pa_{O_2} of only 9 kPa. Facial CPAP at a level of 7.5 cm H_2O was continued and negative fluid balances were obtained by fluid restriction and forced diuresis by loop diuretics. Fluid balance was monitored in the usual way by detailed input/output charts and urethral catheterization. These treatments resulted in reduction of his $F\text{I}_{O_2}$ to 0.45.

On day 9, after internal fixation of his ankle, the patient's lungs were ventilated overnight. Following tracheal extubation the next morning, he was given CPAP at a level of 7.5 cm H_2O by facemask. At this stage he still had a large flail segment, and radiological and clinical evidence of continuing contusion in his left lung. The right basal contusion had now resolved.

Over the next 72 h, the patient developed increasing respiratory distress, with an increasing respiratory rate (up to 50 b.p.m.), shallow breathing and an uneven respiratory pattern, and the $F\text{I}_{O_2}$ had increased to 0.6, in order to maintain a Pa_{O_2} of 10 kPa. On day 12, NIPPV was commenced via a nasal mask (NIPPY2 ventilator, Aeromed, UK), with an immediate reduction in his oxygen requirements. He remained on continuous nasal NIPPV for a further 9 days, with a reducing level of pressure support and CPAP; the NIPPV was tolerated extremely well throughout. His invasive lines were all removed on day 18.

By day 20, he was receiving only intermittent NIPPV, and otherwise had an oxygen saturation (Sa_{O_2}) of 98% on 3 litres min^{-1} of oxygen via nasal cannulae. On day 22, he was given NIPPV overnight only, and the NIPPV was discontinued on day 24. Nocturnal CPAP by facemask continued for a further night, and he was discharged to the ward on day 26.

Apart from a 5-day course of flucloxacillin to treat a *Staphylococcus aureus* infection in a laceration, the patient required no antibiotics during his stay on the intensive care unit (ICU). At no stage was there any evidence of systemic or pulmonary infection.

Discussion

Ventilator-associated pneumonia represents a major subgroup of nosocomial pneumonia, a condition that is associated with a mortality of 30%.[5] In those patients who survive, ventilator-associated pneumonia is associated with increased morbidity, longer ICU stays, and hence increased costs.[6] The pathogenesis of this condition involves bacterial colonization of the upper aerodigestive tract, and hence oropharyngeal secretions. These contaminated secretions pool above the cuff of the tracheal tube, and are aspirated into the trachea during patient movement, coughing, tracheal suctioning and many other manoeuvres.[7–9] Tracheal intubation has indeed been shown to be an important risk factor for the development of ventilator-associated pneumonia,[10] and so it would seem sensible to avoid this if at all possible.[11]

NIPPV has been shown to be as effective as conventional ventilation in a variety of settings, including exacerbations of chronic obstructive pulmonary disease[12] and acute respiratory failure.[13] The causes of the acute respiratory failure in the latter paper ranged from infection and pulmonary oedema to acute respiratory distress syndrome. To date, there have been no reports of the use of NIPPV in severe chest trauma.[14]

Nava *et al.*[12] allocated random patients with exacerbations of chronic obstructive pulmonary disease to either NIPPV or conventional ventilation, after an initial period of 48 h conventional ventilation. Seven out of 25 patients in the conventionally ventilated group developed ventilator-associated pneumonia, compared to none of the NIPPV group (P=0.009). Antonelli *et al.*[13] allocated random patients to either NIPPV or conventional ventilation from the outset. Again, the patients ventilated non-invasively had a significantly lower incidence of ventilator-associated pneumonia and sinusitis. While this study had some minor methodological flaws, it demonstrates a clear difference in infective complications between the two groups, and adds further evidence to the hypothesis discussed above, that avoidance of tracheal intubation reduces the incidence of ventilator-associated pneumonia, and thus decreases length of ICU stay and other variables.[6]

Thoracic injury consists of a spectrum of disease, ranging from rib fractures with mild pulmonary contusion to disruption of the thoracic cage and acute respiratory distress syndrome. Although many of the less severely injured patients are now managed without ventilatory support, with a thoracic epidural and aggressive chest physiotherapy,[14] there will always be a number for whom this is not sufficient. These patients, usually with significant hypoxaemia, often require an extended period of invasive ventilation,[15] and the risk of ventilator-associated pneumonia is thus high. We believe that in this group, avoidance of tracheal intubation and hence avoidance of ventilator-associated pneumonia may be a major step in reducing ICU stay, morbidity and mortality. NIPPV is safe, effective, and, we believe, may be the mode of choice for managing patients with thoracic trauma who have no contraindications to its use. We have since used NIPPV in a further two patients with bilateral flail chest and lesser degrees of pulmonary contusion, and had very similar results with regard to effectiveness of the ventilatory support, and avoidance of ventilator-associated pneumonia.

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Lobectomy for cavitating lung abscess with haemoptysis: strategy for protecting the contralateral lung and also the non-involved lobe of the ipsilateral lung

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We describe the anaesthetic management of a patient undergoing lobectomy for cavitating lung abscess complicated by haemoptysis. Surgery for lung abscess is one of the absolute indications for the use of a double-lumen tube (DLT). Because pus or blood could impede fibreoptic-assisted DLT placement, a traditional, blind placement of the DLT was performed. To protect the uninvolved parts of the operated lung, ventilation of the lung with the abscess was not performed until the resection of the involved lobe had been completed.

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Current management of lung abscess[1–3] in the main involves appropriate antibiotics, physiotherapy and, where indicated, chest tube drainage: thoracotomy tends to be restricted to those cases not responding to intensive and prolonged medical management or those complicated by haemoptysis,[4] empyema, malignancy or suspected malignancy. Thus, unlike the era before antibiotics, today the thoracic anaesthetist has limited experience in anaesthetizing patients with cavitating lung abscesses. One of the main aims of anaesthesia is to protect the so-called good lung from contamination, and the introduction of the endobronchial tube and the double-lumen tube (DLT) in the 1950s overcame the need to employ awkward and inconvenient patient positioning, such as the Parry Brown or the Overholt positions. The former relied upon intra-operative drainage by gravity of infective material via the trachea, while the latter relied upon retention by gravity within the abscess cavity. Now, the use of a DLT or a tube-and-blocker is mandatory during thoracotomy for lung abscess or for frank haemoptysis.[5]

Even so, when planning anaesthesia for a patient with a high risk of purulent material and/or blood draining by gravity into the major airways, the anaesthetist and surgeon still face several dilemmas. First, should the patient stay in the sitting or semi-sitting position until lung separation is achieved? Secondly, what is the operative team's preferred DLT placement plan for such a case? Thirdly, should an effort be made to minimize the dissemination of infective material throughout the operated lung as well as the good lung?

Case report

Pneumonia that had failed to resolve over a 12-month period, in a 32-yr-old previously well woman, led to a consolidated left lower lobe with a large cavitating lung abscess. Early in this disease, she had developed haemoptysis and on many occasions had coughed varying amounts of frank blood, sometimes in excess of an estimated half-teacup. Later, she was coughing purulent sputum streaked with blood. She said that the episodes of haemoptysis were caused by her lying flat, and as a consequence she slept in a sitting position and would not allow herself to be placed otherwise. Such was her fear of further haemoptysis that she refused physiotherapy and totally rejected any suggestion of postural drainage. Her weight decreased from 75 to 46 kg, and she developed marked clubbing of the fingers and toes. The preoperative chest x-ray and CT scan are shown in Figures 1 and 2 respectively.

Extensive investigation failed to identify any underlying pathology. There was no evidence of immunosuppression or aspiration. Bronchoscopy revealed no endobronchial lesion and washings were positive for *Pseudomonas aeruginosa*. She was admitted on several occasions with fever, increas-

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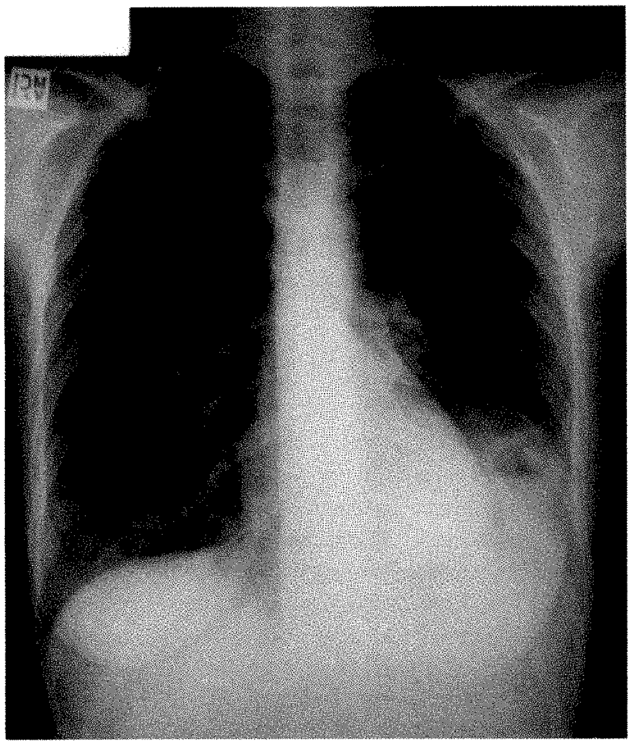

Fig 1 Posteroanterior chest x-ray revealing a left lower lobe opacity and an abscess with fluid level.

ing dyspnoea and/or haemoptysis, and although on each occasion there was a response to broad-spectrum intravenous antibiotics, lobectomy was advised when the haemoptysis became more voluminous and she became significantly anaemic. The favoured preoperative diagnosis was either localized bronchiectasis or pulmonary sequestration. Histopathology of the resected lobe revealed an actinomycosis abscess but no other underlying abnormality.

The patient was anaesthetized in a semi-sitting (50° head-up) position, with meticulous preoxygenation, midazolam 1 mg, fentanyl 200 µg in divided doses, an initial dose of propofol 80 mg and rocuronium 40 mg. While the patient was maintained in the 50° head-up position, gentle hand ventilation with oxygen was performed for 3 min. The patient was then placed horizontally and, without further ventilation, elective rigid bronchoscopy was performed by the surgeon to assess bronchial anatomy/pathology and to perform tracheobronchial suction. An estimated 3 ml of purulent material was removed by direct suction from the trachea and airways, and the surgeon advised that the major airways were small.

In the light of this comment, and with fibreoptic bronchoscope and left and right Robertshaw DLTs immediately at hand, a 35 FG Left Sheridan DLT was inserted blind, to the perceived desired depth. Inflation of the bronchial cuff to a tension greater than usual in the 5 ml inflating syringe and the pilot cuff was achieved with a relatively small volume of air. Cautious hand ventilation via a single catheter-mount connected to the DLT bronchial lumen was observed to produce left chest movement. Transfer of ventilation to the tracheal lumen produced right chest movement, and the tracheal cuff was inflated to produce a seal. Next, the single catheter mount was transferred back to the bronchial lumen and auscultation over the anterior apical region of the left chest during gentle hand ventilation confirmed the presence of vesicular breath sounds. From that point onward, single-lung intermittent positive pressure ventilation was restricted to the right lung until the left lower lobe resection had been completed. During the period when it was not ventilated, the left lung was connected to a 3-litre oxygen reservoir at ambient pressure.[6] For reasons that will be discussed, the fibreoptic bronchoscope was not used either before or after positioning the patient for surgery.

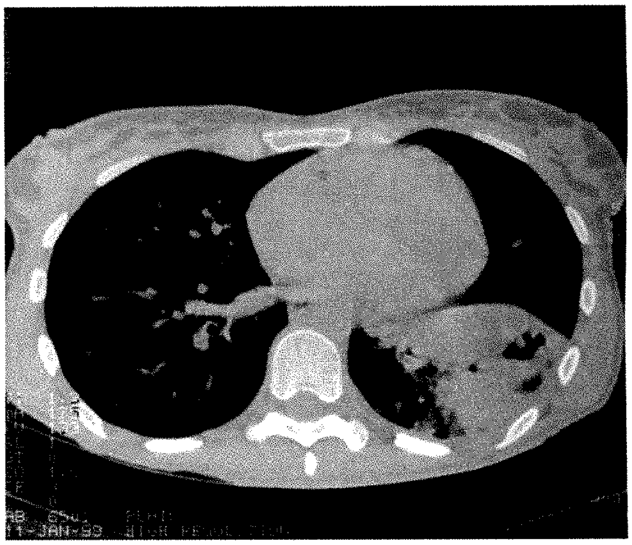

Fig 2 CT chest scan at the level of the apical segment of the left lower lobe, revealing consolidation and cavity formation.

During the chest incision and until the thoracic cavity was opened, the reservoir bag was seen to distend and collapse as expected with each cycle of single-lung ventilation to the dependent lung.[6] This tidal movement of the reservoir bag was in this case less pronounced than usual and, although this was most likely a consequence of the left lower lobe pathology, the possibility of distal migration of the DLT to occlude or partially occlude the left upper lobe bronchial orifice was also considered. However, because the peak and plateau inflation pressures in the ventilated dependent right lung were as expected and because there was no reduction in pulse oximetry while performing single-lung ventilation with a fresh gas flow of 50% N_2O/O_2, no intervention was thought necessary or justifiable. This decision was vindicated by prompt left upper lobe collapse when the chest was opened and easy re-expansion when the surgery was completed.

Once the chest was opened and the operated lung was able to collapse down, the oxygen reservoir was temporarily detached from the bronchial lumen of the DLT while further purulent material was removed by suction. Only then was some air cautiously removed from the DLT bronchial cuff to return it to a more usual tension. This was performed whilst listening with an ear pressed to the reservoir bag in order to immediately identify possible gas leakage past the cuff during the inspiratory phase of ventilation.[6]

At surgery, the left lower lobe was distended and also patchily consolidated. It was densely adherent over a large part of its diaphragmatic surface, but, apart from the need to divide these adhesions, the lobectomy was uneventful and the chest was closed with an apical and a basal drain. Before the re-expansion of the left upper lobe, the bronchial tree on that side was again cleared by suction via the DLT bronchial lumen. At this time it was noticed that a considerable volume of purulent material had drained from the operated lung, filling the DLT bronchial lumen and extending into the tubing leading to the reservoir bag.

Throughout the period of single-lung ventilation and an FI_{O_2} reading of approximately 0.4, the Sp_{O_2} remained between 98 and 100%.

Postoperative recovery was uneventful, and the patient was able to lie happily in whatever position she liked.

Discussion

With a cavitating lower lobe abscess, the first dilemma facing the anaesthetist and surgeon is whether or not to aim to achieve DLT lung separation while the patient is maintained in a steep sitting or semi-sitting position. With the case described, this decision was influenced by the fact that a preoperative rigid bronchoscopy was planned in order to make a surgical assessment of the pathology, to clear secretions and to identify any atypical bronchial anatomy. Conacher has said for the same reasons, with regard to the need for rigid bronchoscopy in the assessment or therapy of bronchopleural fistula, that 'most experienced personnel prefer to base the anaesthetic technique around this requirement'.[7]

For the rigid bronchoscopy, the patient was anaesthetized in the semi-sitting position (about 50° from horizontal) but was put in the horizontal position with the onset of good muscle relaxation. The bronchoscopy and bronchial suction under direct vision were performed without delay, and no further ventilation was performed until after the DLT was positioned and the bronchial cuff inflated. Even so, some management teams might strive to retain the patient in the semi-sitting position for the bronchoscopy and until such time as lung separation is secured.

The course of action chosen depends on the preferred practice of the individual surgical/anaesthesia team and by the clinical circumstances of the individual patient. Rigid bronchoscopy with the patient 50° head-up used to be the accepted management for sputum retention after pulmonary resection, but today it is a disappearing skill. Any partial reduction of the degree of head-up tilt of our patient might well have resulted in spillage of infective material into the lower lobe bronchus of the 'good' lung.

Alternatively, performing or attempting to perform fibreoptic assessment and fibreoptic-assisted intubation with a patient maintained in the sitting position can be difficult or prolonged if secretions obscure vision.

Should suxamethonium have been used? Probably not in this patient, but it would certainly be advisable in any patient in whom difficulties might be expected with gentle face-mask hand-ventilation.

Should anaesthesia have been induced with the patient sitting on the horizontal lower half of an operating table that is broken at the mid-point, with the patient's thorax reclining, abscess-side dependent, against the steeply angulated upper half? Probably, yes! Once asleep and paralysed, the patient could easily have been maintained abscess-side dependent, and the head-up tilt could have been reduced if necessary to facilitate bronchoscopy and intubation.

The next dilemma relates to the choice of DLT and the plan for its placement. The necessary decisions will depend on previous experience and preferences. In this case, a range of DLTs and a fibreoptic bronchoscope were immediately at hand. The first management option was the blind placement of a 35 FG Left Sheridan DLT, because it was felt that pus or blood might obscure the view at fibreoptic bronchoscopy. A plastic tube was chosen in preference to a Robertshaw DLT because the external diameter of a medium Robertshaw could have been too tight for the reputedly small airways. Otherwise, the more firmly anatomically shaped Robertshaw tube would have been chosen. This DLT frequently appears to drop into place and, in the authors' view, is less likely to become dislodged by surgical traction in the course of the operation.

If the left-sided Sheridan DLT had entered the right rather than the left main bronchus, the plan was to replace it immediately with a medium or small left Robertshaw. If the left Robertshaw had also entered the right main bronchus, it was to have been replaced immediately with a right Robertshaw. Use of the fibreoptic bronchoscope to guide one of the left-sided clear plastic tubes down the left main bronchus was considered as a last resort in our team's order of priorities for this particular patient. However, since a plastic and not a Robertshaw DLT was being used, a good case could have been made for positioning a fibreoptic bronchoscope down the tracheal lumen and observing, if secretions had permitted, the passage of the bronchial component into the left main bronchus.[8,9]

A conscious decision was made not to check DLT placement with the fibreoptic bronchoscope that was immediately at hand. The small volume of air injected into the bronchial cuff of the left-sided DLT to produce an airtight seal, the free gas movement in and out of the right lung and the confirmation of vesicular breath sounds in the left upper lobe by the anaesthetist who was also performing the gentle hand ventilation were considered assurance enough. With these findings and in this particular case, the anaesthetist would not have deflated the cuffs and pulled back the tube, even if bronchoscopy via the DLT tracheal lumen had failed to reveal any sign of the bronchial cuff.

The third dilemma relates to the protection of the healthy parts of the lung that contains the abscess. The frequent removal of secretions during surgery by suction via the DLT lumen on the diseased side is the standard recommendation.[5] A further and not previously reported measure is to refrain from ventilating the lung with the abscess until the risk of contamination is removed. If adopted, this will involve a period of single-lung ventilation while the chest is being opened and hence before the non-ventilated lung is able to collapse away from the chest wall. We recommend that the airway of the non-ventilated lung is connected to an ambient-pressure oxygen reservoir to prevent ambient air and therefore nitrogen from entering the non-ventilated lung.[10] This practice has several benefits, both theoretical and practical.[6]

One of the possible theoretical benefits while the patient is being positioned ready for surgery and while the chest is being opened is the oxygenation of the blood that continues to flow through the non-ventilated but not yet collapsed lung. This results in an atypical ventilation/perfusion mismatch, with good oxygenation of the shunted pulmonary blood flow but with no elimination of carbon dioxide once the $P\text{CO}_2$ of gas in the reservoir bag has equilibrated with that of the mixed venous blood. This atypical mismatch will in theory be expected to result in a small further increase in the relatively large arterial to end-tidal carbon dioxide gradient seen during thoracic anaesthesia.[11] Thus, if there is a delay in opening the chest and hence a delay in lung collapse, arterial blood gases may be required to guide the level of minute volume ventilation.

In the case presented, an additional practical benefit of the ambient-pressure oxygen reservoir was demonstrated. Once the chest was opened and surgery was progressing, the anaesthetist was able, by listening with the ear pressed against the reservoir bag,[6] to deflate the bronchial cuff carefully to a more usual tension without risk of creating an unidentified loss of the airtight seal.

The small tidal movement in the reservoir bag before the chest was opened was probably caused by the pathological process in the left lower lobe, and by infective material draining by gravity and obstructing or partially obstructing major airways on that side. It may also have been partly a consequence of dependent lung ventilation causing mainly diaphragmatic rather than mediastinal displacement in this very thin patient.[10]

In conclusion, anaesthesia for thoracotomy for cavitating lung abscess, with or without a history and hence risk of haemoptysis, should involve preoperative physiotherapy to reduce secretions, appropriate patient positioning with the lobe containing the abscess dependent relative to the rest of the bronchial tree, careful preoxygenation, and an anaesthesia plan that achieves prompt lung separation. Elective rigid bronchoscopy before DLT placement allows both surgical assessment of bronchial pathology and anatomy, and the efficient removal of secretions or pus. Once lung separation is achieved, not ventilating the lung with the abscess may reduce the risk of contamination of healthy parts of this lung. While the lung containing the abscess is not being ventilated, there are both theoretical and practical benefits in connecting this lung to an oxygen reservoir at ambient pressure. After the diseased lobe has been excised, suction via the DLT lumen on that side before re-expansion of the residual lobe will remove any purulent material that has drained from the abscess in the course of surgery.

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Adult epiglottitis: an under-recognized, life-threatening condition

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Epiglottitis in the adult can be fatal and should be treated with the same degree of concern and suspicion in respect of airway patency as in children. We present three cases of adult epiglottitis in which the airway was lost prior to or during the intervention of an anaesthetist. We suggest that an emphasis on conservative management is distracting and belies the serious nature of this disease.

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Epiglottitis is an inflammation of the supraglottic structures that can occur at any age. There is a reported increase in the incidence of epiglottitis in the adult population.[1] In contrast to the aggressive management of epiglottitis in children, a more conservative approach has been advocated in adults.[2] We present three cases of adult epiglottitis where the airway was lost either before or during intervention of an anaesthetist.

Case reports

Case 1

A 41-yr-old male presented with a sudden onset of sore throat, stridor and dyspnoea. He was previously fit but regularly smoked heroin. On arrival to the accident and emergency department, he rapidly developed complete airway obstruction resulting in a respiratory arrest. Manual ventilation by facemask proved ineffective and no i.v. access could be secured. Laryngoscopy was impossible because of trismus. Intralingual succinylcholine 100 mg was injected and permitted laryngoscopy. A large mass arising from the epiglottis was observed, completely obscuring the larynx. Following oxygenation via an emergency cricothyroidotomy, the trachea was intubated nasally using a fibreoptic bronchoscope. Intravenous cefotaxime was commenced. A surgical tracheostomy was performed under general anaesthesia and the patient admitted to a high dependency area on the otolaryngology ward. A lateral soft tissue neck radiograph (Fig. 1), MRI scan (Figs 2 and 3) and fibreoptic nasendoscopy (Fig. 4) were performed once the airway had been secured. The patient made a full recovery. *Candida albicans* was eventually cultured from the mass.

Case 2

A 73-yr-old male was admitted with less than a 24-h history of sore throat, dysphagia and dyspnoea associated with mild inspiratory stridor. Fibreoptic nasendoscopy in the accident and emergency department revealed a swollen, hyperaemic epiglottis. Blood cultures were taken and he was commenced on i.v. cefotaxime and dexamethasone 4 mg. Four hours later, on the otolaryngology ward, his respiratory status deteriorated rapidly. A surgical tracheostomy was attempted under local anaesthesia but the procedure abandoned when the patient became hypoxic and began convulsing. The anaesthetist was able to intubate the trachea orally in the unconscious patient, prior to transfer to the operating room for conventional tracheostomy. The patient was admitted to the intensive care unit and made an uneventful recovery. The trachea was decannulated 4 days later. Two blood cultures taken on the day of admission both grew *Neisseria meningitis*, later typed as Group Y. There was no other positive microbiology and virology screen was normal.

Case 3

A 56-yr-old man was admitted to the accident and emergency department with acute onset of a sore throat and dysphagia. He was sitting up, dyspnoeic, and drooling saliva. A flexible nasendoscopy showed an oedematous, enlarged epiglottis. An i.v. line was inserted, blood cultures taken and Augmentin 1.2 g and hydrocortisone 200 mg were given intravenously. The patient was transferred to the operating theatre. During an inhalational induction of anaesthesia with sevoflurane, he developed complete airway

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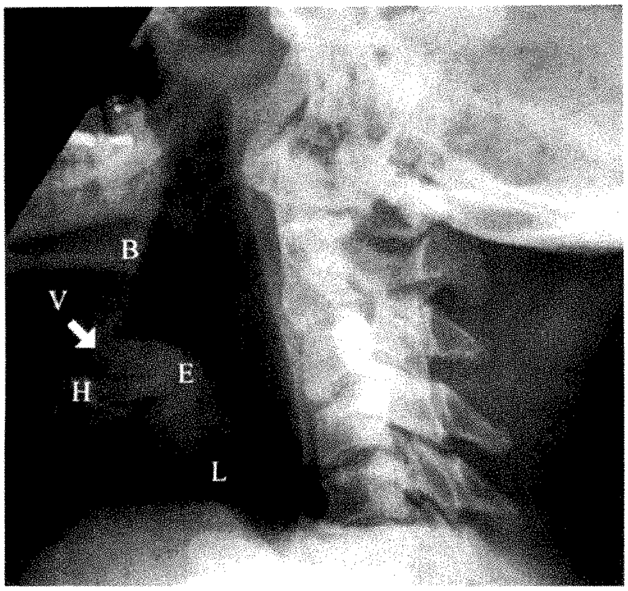

Fig 1 Lateral soft tissue radiograph demonstrating the 'thumb print' sign (E). The 'vallecula' sign (V) can be determined by identifying the base of tongue (B) and tracing it inferiorly to the hyoid bone (B). If there is no pocket of air extending almost to the hyoid bone and roughly parallel to the pharyngotracheal air column, then the diagnosis of epiglottitis is confirmed. Laryngeal inlet is noted (L).

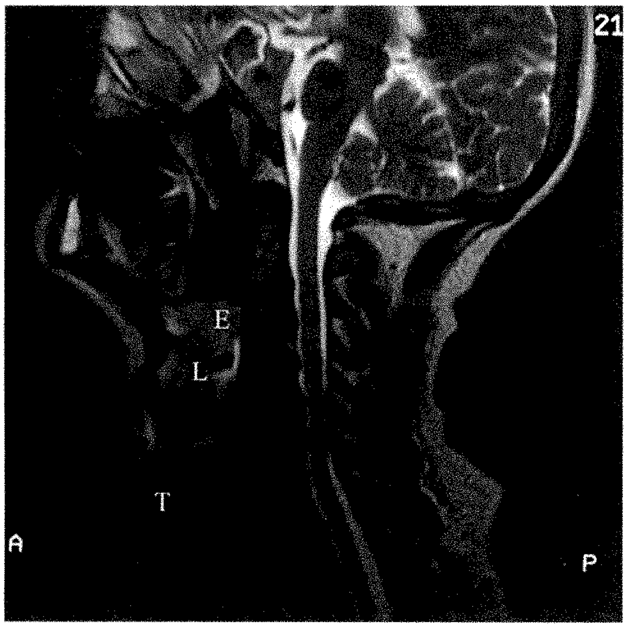

Fig 2 Sagittal MRI of case 1. The prominent swollen epiglottis (E) is clearly visible above the laryngeal inlet (L). The tracheostomy (T) is also noted.

obstruction. Intravenous succinylcholine 100 mg was administered and orotracheal intubation was attempted but failed. An emergency cricothyroidotomy was then performed using a 13-gauge transtracheal catheter. Jet ventilation was commenced and continued whilst a surgical tracheostomy was performed. The trachea was decannulated 3 days later. Blood cultures were negative.

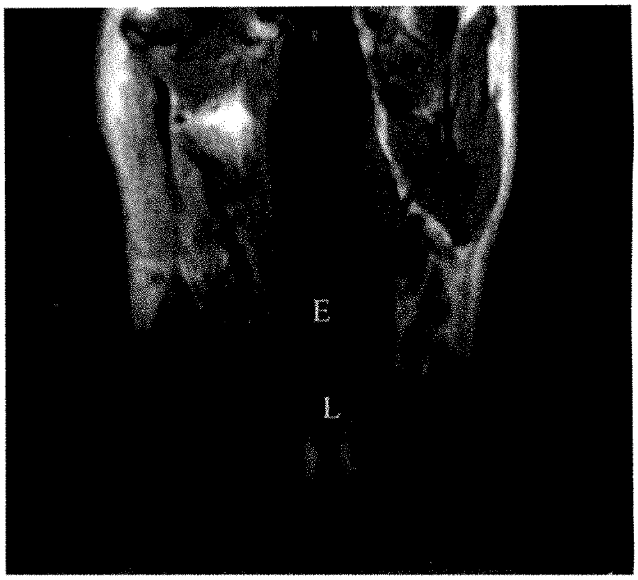

Fig 3 Coronal MRI of case 1. Again the enlarged epiglottis (E) can be seen above the laryngeal inlet (L).

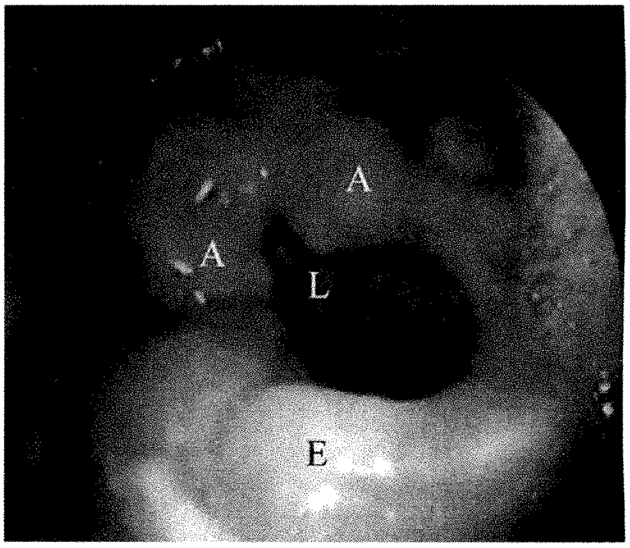

Fig 4 Fibreoptic nasendoscopy view in case 1. Unlike the classic cherry red epiglottis in children, adult epiglottitis is characterized by diffuse inflammation of aryepiglottic structures. Both the epiglottis (E) and the arytenoids (A) are clearly inflammed. The laryngeal inlet (L) is noted.

Discussion

Adult epiglottitis has an incidence of between 1–4 per 100 000 per annum[3,4] and is described as having a low morbidity and mortality.[5] Nonetheless, mortality in adults is around 7%, and some reports suggest it is as high as 20%.[3] Hingorani and colleagues[6] observed that a similarly high mortality in children prompted a change to an interventional practice. Even though adult epiglottitis is unpredictable and occasionally catastrophic in outcome, conservative management is still preferred by many authors.[2,5]

Haemophilus influenzae type B is found in as few as 17% of adult patients with suspected epiglottitis.[7] There is also a high rate of negative blood cultures possibly suggestive of a viral cause (although only herpes simplex has been reported).[5] Meningococcal epiglottitis is extremely rare and we present only the seventh reported case; the first was reported in 1995.[8] Alternatively, epiglottitis may occur following mechanical injury such as the ingestion of caustic material or the inhalation of hot objects, smoke or vapours. Epiglottitis following illicit drug use has been described as a result of the accidental inhalation of a heated objects.[9] Although there has been an association with cigarette smoking,[10] there are no reports linking epiglottitis and the smoking of heroin. The causal organism or factor is, therefore, often less identifiable in adults than in children.

An adult with epiglottitis usually presents with symptoms of sore throat and painful dysphagia.[3] Drooling and stridor are infrequent presenting signs. In fact the presence of stridor, dyspnoea and a short duration of symptoms prior to presentation, are all described as predictors of airway loss in the adult with epiglottitis.[4 10] This is, however, controversial. For example, Wolf[2] presented 30 patients in whom stridor was present and who were subsequently successfully treated conservatively. On the other hand, Mayo-Smith described a patient who had no history of stridor, yet suddenly developed airway obstruction and died.[11] Indeed the three cases we present support the fact that the disease presentation and progression is variable and that there are no reliable markers that predict the need for invasive airway support.

The diagnosis of epiglottitis is essentially clinical but can be supported by indirect laryngoscopy. Typically, there is diffuse swelling of the aryepiglottic structures unlike the classic cherry red epiglottis in children. Otherwise, once the airway is deemed safe, a lateral, soft tissue radiograph may show a thickening of the epiglottis ('thumb print sign'; see Fig. 1). Ducic and colleagues have proposed the 'vallecula sign' to improve the diagnostic accuracy of soft tissue radiographs.[12] This stepwise approach attempts to identify the vallecula as it nears the level of the hyoid bone. In the absence of a 'deep and well-defined vallecula', the radiological findings support the diagnosis of epiglottitis.

If the clinical diagnosis of epiglottitis is made and the airway judged to be at risk, intervention should not be delayed by attempts to obtain cultures or radiographs. Treatment should begin promptly with intravenous antibiotics. Steroids have no accepted place and the benefit of epinephrine, either nebulized or intramuscular, has yet to be confirmed.

Either orotracheal intubation or tracheostomy may be performed under local anaesthesia but both are potentially stimulating procedures which may precipitate sudden loss of the airway. General anaesthesia may be performed with an inhalational induction but can be complicated by a relatively prolonged excitation phase in adults (as occurred in case 3). Friedman therefore recommended a rapid sequence induction with the facility to perform a cricothyroid puncture if intubation proves difficult.[13] Bag and mask ventilation can simply worsen or complete the airway obstruction and should be avoided.

Neuromuscular blocking drugs are traditionally avoided in epiglottitis (although succinylcholine was listed on a recent protocol for the management of paediatric epiglottitis[14]). We used succinylcholine in two of the above case reports, including one intralingual injection. Although this route is described in children, we could find no reference to its use in adults.

In summary, a belief that epiglottitis is rare in adults has contributed to misdiagnosis and high mortality rates. We present three cases that are typical of adult epiglottitis, in that there is no one identifiable causal agent or factor that would allow rationalisation of a particular therapy. To advocate conservative management belies the aggressive nature of this disease. We believe there should be a greater emphasis on early interventional support of the airway.

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Falsely elevated bispectral index during deep hypothermic circulatory arrest

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A 2-month-old infant underwent repair of a ventricular septal defect under deep hypothermic circulatory arrest. Bispectral index and EEG suppression ratio were evaluated using an Aspect BIS monitor. Erroneous readings from the monitor could have led to a potentially dangerous alteration in surgical and anaesthetic management.

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The bispectral index (BIS) is rapidly gaining acceptance as a measure of hypnosis under anaesthesia. Additionally, the BIS monitor unit can be used as a readily available and easily interpreted tool to ensure EEG burst suppression during deep hypothermic circulatory arrest. This is displayed as a suppression ratio, which is the percentage of time during the preceding 60 s in which EEG burst suppression occurred. We report a case where a BIS monitor (Aspect Medical Systems, Spotsylvania, VA, USA) demonstrated erroneous readings during deep hypothermic circulatory arrest that could have altered the anaesthetic and surgical management of the patient.

Case report

A 2-month-old, 3 kg male patient presented to the cardiac surgery service for repair of a ventricular septal defect (VSD). Cardiac catheterization revealed a large muscular VSD with a pulmonary to systemic blood flow ratio of greater than 4 to 1. The patient was medically managed with digoxin and furosemide and had no clinical evidence of congestive heart failure at the time of surgery.

After placement of standard, non-invasive monitors, the patient was anaesthetized with fentanyl, 10 $\mu g\ kg^{-1}$, vecuronium, 0.1 mg kg^{-1}, 30% oxygen in nitrous oxide, and isoflurane, 0.5–2.0 vol%. Anaesthesia was maintained with the volatile agent and occasionally supplemented with fentanyl and vecuronium. Additional monitors placed after induction included a femoral arterial catheter, internal jugular triple lumen catheter, Aspect model A-2000 BIS monitor (system revision 0.41) and cerebral venous oximeter (Somanetics Corporation, Troy, MI, USA). In preparation for deep hypothermic circulatory arrest, methylprednisolone, 10 mg kg^{-1} was administered and the head was packed in ice. Following anticoagulation with heparin, aortic and right atrial cannulae were placed and cardiopulmonary bypass (CPB) was started. At the start of CPB the BIS was in the 40s. The patient was cooled to a core temperature of 18°C and deep hypothermic circulatory arrest was instituted after 15 min of cooling time on CPB. At the time of deep hypothermic circulatory arrest the BIS was zero with a suppression ratio of 100. The cerebral mixed venous oxygen saturation (Sr_{O_2}) had increased from baseline by more than 100% during cooling.

Within the first 5 min of deep hypothermic circulatory arrest, the Sr_{O_2} decreased to baseline. By 15 min of deep hypothermic circulatory arrest the Sr_{O_2} had decreased over 50% from baseline and was below the limits of measurement. The patient's core temperature had started to slowly drift upward and by this time had reached 22°C. At 16 min of deep hypothermic circulatory arrest the BIS abruptly increased to 98–100, with a suppression ratio of 0–10 (Fig. 1). The raw EEG tracing on the BIS monitor appeared flat and unchanged. The EMG readout on the monitor throughout CPB was negligible. The surgeon was advised of the monitor readings and was asked to resume CPB as soon as possible. The repair was expedited and the patient returned to CPB within 5 min. Immediately on return to CPB, the Sr_{O_2} again increased to over 100% of baseline. After approximately 10 min of rewarming the BIS returned to its pre-deep hypothermic circulatory arrest level in the 40s. The patient was weaned from CPB and the procedure concluded without further incident. He was

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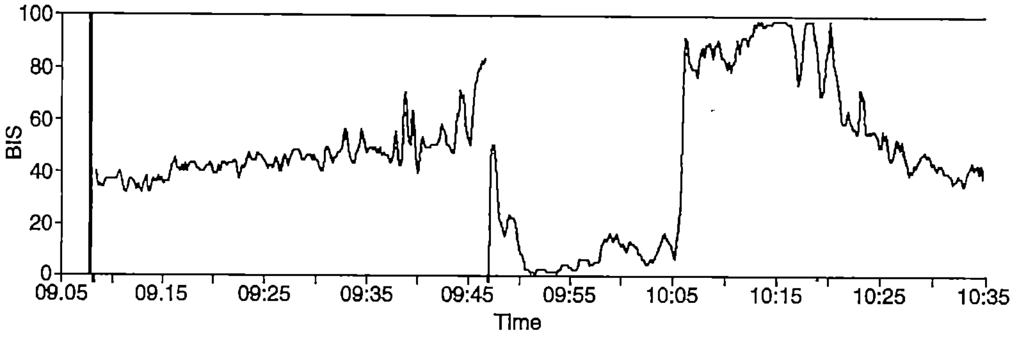

Fig 1 Printout of BIS values during case. Note BIS in 40s at start of CPB, 09.35 h. BIS decreased to 00 by start of deep hypothermic circulatory arrest, 09.50 h. BIS abruptly increased to 98–100 at 10.06 h, with return to baseline starting at 10.16 h as rewarming continued.

extubated the next morning having suffered no apparent neurological sequelae.

Discussion

The bispectral index is an artificial variable arrived at by computer processing of, most commonly, a one-channel EEG pattern via a proprietary algorithm of the Aspect Corporation. This value, scaled from 0 to 100 reflects a patient's level of hypnosis, and potentially, probability of recall.[1] This has become an important, if somewhat emotionally charged, anaesthetic safety issue in the last few years. Some have even speculated that BIS monitoring will become the next 'standard of care'.[2] This has led to a rapid proliferation in the number of BIS monitors available in operating rooms across the USA. The Aspect monitors, the only presently available, are easy to use and interpret, requiring very little time to fully orient and train most anaesthesia practitioners. An added advantage of the Aspect monitors is their ability to display real-time EEG tracings, accompanied by the suppression ratio. With the caveat that this offers a very limited picture of the total brain EEG activity, the BIS monitors are thus a readily available and easily used EEG processing system for the detection of gross global changes.

EEG monitoring during deep hypothermic circulatory arrest is of controversial benefit. It has been suggested that outcome is improved when EEG burst suppression is achieved by cooling.[3] Burst suppression has been used as an indicator of adequate brain protection during deep hypothermic circulatory arrest.[4] There are other studies, however, which do not demonstrate improved outcome from use of EEG monitoring.[5] As a result of these issues, coupled with the logistical and economic pressures of equipment and personnel availability, EEG monitoring during deep hypothermic circulatory arrest is not applied universally and varies greatly among institutions. The wide availability and ease of use of the Aspect BIS monitors obviates some of these concerns. Although its benefit has not been demonstrated in peer-reviewed studies, the suppression ratio detected by BIS monitors may be of value in helping to assess optimal brain protection prior to deep hypothermic circulatory arrest.

In this case the brain was cooled for 15 min prior to deep hypothermic circulatory arrest. The period of cooling was somewhat shorter than the usual practice at this institution, and was dictated by the surgeon as he felt the arrest time would be very brief for anatomic reasons. This appeared to have the desired result of metabolic suppression, as evidenced by the significant increase in Sr_{O_2}. Appropriately, the BIS decreased while the suppression ratio increased, correlating with EEG suppression induced by cooling. The rapid decrease in Sr_{O_2} following deep hypothermic circulatory arrest, however, was disturbing and suggested a possible depletion of oxygen stores in the brain, which may be seen following heterogeneous cooling, especially following an abbreviated cooling time. As the temperature drifted upward, the BIS increased abruptly to high levels at 23°C after 16 min of deep hypothermic circulatory arrest. The most worrisome thought was that this could possibly represent the monitor's interpretation of seizure EEG secondary to anoxic insult. The surgeon was advised of these concerns, but this was tempered by the real-time EEG waveform, which appeared to be highly suppressed. It was our impression that this was most likely an artefactual product of the algorithm's misinterpretation of EMG activity or other radiofrequency interference. The ice surrounding the patient's head was wrapped in plastic and towelling, thus increased electrode impedance was not thought to be a factor. The surgeon quickly completed the repair and the patient was returned to CPB. When the brain had been rewarmed, the BIS returned to pre-cooling levels, further reinforcing our belief that this was an artefact, although amelioration of seizure activity by improved perfusion remained a possibility. In approximately 30 deep hypothermic circulatory arrest cases prior to the one reported, the BIS had not displayed this activity, but rather remained highly suppressed until the brain had been rewarmed. It has also not appeared in the 10 cases subsequent to the case reported. In the postoperative period the patient demonstrated no evidence of neurologic insult and was discharged home after an uneventful recovery.

Both EMG activity and radiofrequency interference from electrical equipment in the operating theatre influence the BIS algorithm. Under normal conditions, the EEG is of sufficient power to override these other electrical sources and is thus weighted appropriately by the algorithm. In circumstances of extreme EEG suppression, as during deep hypothermic circulatory arrest, it is possible that electrical interference from either EMG or radiofrequency noise may be interpreted by the algorithm as EEG activity and assigned a high BIS value. When EEG activity resumes, as during rewarming, the monitor then re-interprets it appropriately, discounting the EMG and radiofrequency activity in the algorithm (personal communication, David Zaraket, Aspect Corporation). This appears to have happened in our case, as there was no demonstrable evidence of neurologic insult, such as seizure activity or choreoathetosis, seen postoperatively.

In conclusion, we present a case where electrical interference was misinterpreted as EEG activity by an Aspect A-2000 BIS monitor during a period of intense EEG suppression. This misinterpretation was displayed as a high BIS value with a low suppression ratio. Observation of the real-time EEG waveform suggested that this was an artefact, but was not absolutely conclusive. During periods of significant EEG suppression, BIS monitors may misinterpret electrical interference as EEG and could possibly lead to unnecessary therapeutic interventions. Observation of the real-time EEG waveform may aid in the diagnosis of this artefact, which, in our experience, occurs infrequently. Further studies are necessary to determine if monitoring suppression ratio and BIS during deep hypothermic circulatory arrest is beneficial and cost effective.

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Perioperative management of a patient requiring surgery for pituitary apoplexy and severe angina pectoris

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We describe the management of a 71-yr-old man with pituitary apoplexy and severe angina pectoris who underwent treatment of an intra-cranial haemorrhage and open-heart surgery requiring anticoagulant therapy within a very short period. Subtotal removal of the pituitary tumour was undertaken under stable cardiovascular conditions. But ventricular fibrillation occurred after the neurosurgery in the intensive care unit. After the patient was defibrillated, intra-aortic balloon pumping was necessary to assist coronary artery blood flow. Twenty hours after neurosurgery, oozing from the surgical wound stopped and coronary artery bypass grafting with full heparinization was performed uneventfully.

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Pituitary apoplexy is a clinical syndrome of sudden haemorrhagic necrosis of the pituitary gland.[1 2] Subsequently, tumour expansion causes headache, visual field deficit and ophthalmoplegia. Recovery of the patient depends on the duration and severity of symptoms. Surgical treatment of intracranial haemorrhage is recommended immediately after appearance of the neurological symptoms.

We experienced a rare case of a patient with pituitary apoplexy coexisting with severe angina pectoris, which required urgent coronary artery revascularization. However, anticoagulant therapy for cardiopulmonary bypass (CPB) might have induced intra-cranial haemorrhage. Pituitary apoplexy has been reported to occur following coronary artery bypass grafting.[3–7] Sequential management of the intracranial haemorrhage and open-heart surgery requiring anticoagulation present a challenge to the anaesthetist.

Case report

A 71-yr-old man (weight 54 kg) was referred to our hospital for surgical treatment of severe triple-vessel coronary artery disease. On admission, he was suffering frequent episodes of angina pectoris at rest requiring treatment with nitroglycerine (0.3 μg kg^{-1} min^{-1}), diltiazem (0.06 mg kg^{-1} h^{-1}) and lidocaine (1 mg kg^{-1} h^{-1}) i.v. He had a past medical history of hypertension and a myocardial infarction.

A pituitary tumour had been diagnosed by cranial computed tomography (CT) 2 days before admission. He had had a slight headache but no other neurological deficits. In hospital awaiting cardiac surgery, he became comatose and was found to have a Glasgow Coma Score (GCS) of 6. Neurological examination revealed dilated bilateral pupils, a visual field deficit, ophthalmoplegia and proptosis. Review of the CT showed a fairly large, iso-dense and high-density sellar mass with haemorrhage. The tumour extended into the suprasellar cistern with compression of the optic nerves and cavernous sinus on both sides. There was haemorrhage into the ventricle and brain tissue.

He underwent emergency neurosurgery before cardiac surgery. In the operating room, invasive blood pressure, central venous pressure, pulse oximetry, end-tidal carbon dioxide and the electrocardiogram were monitored. Anaesthesia was induced with midazolam 2 mg and fentanyl 200 μg. Pancuronium 8 mg was administered to facilitate tracheal intubation. Anaesthesia was maintained with 0.5–2% sevoflurane and an i.v. fentanyl (2 μg kg^{-1} h^{-1}) infusion, and muscle relaxation was maintained with intermittent boluses of pancuronium. Mechanical ventilation with a tidal volume of 10 ml kg^{-1} and respiratory rate of 12 min^{-1} was adjusted to maintain normocapnia. Dopamine 3–7 μg kg^{-1} min^{-1}, nitroglycerine 0.15–0.7 μg kg^{-1} min^{-1}, diltiazem 0.06–0 1 mg kg^{-1} h^{-1} and lidocaine 1 mg kg^{-1} h^{-1} were administered continuously throughout surgery. After bifrontal craniotomy, the neurosurgeon approached the tumour inter-hemispherically and performed subtotal tumour resection. The 10-h surgery was completed without complication and with a blood loss of only 300 ml. Examination of the surgical specimens revealed haemorrhagic and necrotic pituitary tissue. After surgery, the patient was haemodynamically stable and was transferred to an intensive care unit, where he was ventilated mechanically and sedated with midazolam. When suctioning was performed through the tracheal tube, ventricular fibrillation suddenly occurred. The patient was cardioverted, additional lidocaine (1 mg kg^{-1}) was administered and sinus rhythm returned. However, premature ventricle complexes occurred frequently and systolic blood pressure was below 90 mm Hg. An intra-aortic balloon pump was placed through the left femoral artery to assist coronary artery blood flow. We did not use any anticoagulant to prevent bleeding from the surgical site. We delayed cardiac surgery for about 20 h after neurosurgery until oozing from the subcutaneous drainage site stopped. The CABG procedure was then undertaken. Upon arrival in the operating room, a pulmonary artery catheter was placed via the internal jugular vein. Anaesthesia was induced with midazolam 2 mg and fentanyl 100 μg, then maintained with propofol 2 mg kg^{-1} h^{-1} and fentanyl 2 μg kg^{-1} h^{-1} intravenously. Muscle relaxation was obtained with pancuronium 6 mg and maintained with intermittent boluses. The patient continued to receive dopamine, nitroglycerine, diltiazem and lidocaine at the same doses until starting CPB The duration of aortic clamping was 60 min and that of CPB was 100 min. The patient was weaned from CPB uneventfully, but balloon pump was continued. Mechanical ventilatory support was continued in the intensive care unit. On the second day postoperatively, CT brain revealed no haemorrhage. The patient regained airway reflexes and spontaneous ventilation. The trachea was extubated. A week after neurosurgery, diabetes insipidus developed and was treated with vasopressin 10 u. day^{-1} intravenously. For about a month after the CABG procedure, his conscious state fluctuated between somnolence and delirium. When delirious, the patient was sedated by a midazolam 1–2 mg h^{-1} infusion.

Within a month, he recovered and had a GCS of 14. Visual field deficit and ophthalmoplegia gradually improved.

Discussion

Pituitary apoplexy is due to an intra-cranial tumour, into which haemorrhage produces an expanding mass, causing visual and neurological impairment. The patient requires neurosurgical treatment immediately. Severe unstable angina with the necessity for an urgent CABG procedure coexisted with the pituitary expansion in this patient. It is often suggested that non-cardiac surgery and CABG should be performed simultaneously.[8 9] In this case, however, anticoagulant therapy with CPB would have induced intra-cranial haemorrhage and the neurological prognosis could have been worse. Confronted with such conflicting situations, we had a dilemma regarding the best surgical management.

In patients with severe angina pectoris and a history of myocardial infarction, the risk of perioperative cardiac complications including death is increased. The American Heart Association reported that the frequency of myocardial infarction and death during simultaneous carotid endarterectomy and a CABG procedure is lower than in a staged operation.[10] Allie and colleagues recommended that a rapid staged procedure (an interval between endarterectomy and CABG procedure of less than 24 h) with intra-aortic balloon pumping was safe and effective in the very high risk patient population with coronary artery disease.[11] But the optimal strategies for the management of patients with carotid and coronary artery disease have not been established. In this patient, the neurological prognosis depended on immediate neurosurgical decompression. We, therefore, performed neurosurgery before the CABG procedure as a staged operation.

The point at which intra-cranial haemostasis is achieved after neurosurgery remains uncertain. Wijdicks reported that restarting anticoagulation therapy in a patient with mechanical heart valves is safe 1–2 weeks after intracranial haemorrhage.[12] However, in this patient, we could not delay the CABG procedure because the patient had ventricular fibrillation and required mechanical support using intra-aortic balloon pumping. When the oozing from the neurosurgical wound stopped, we immediately performed the cardiac surgery using anticoagulant therapy 20 h after neurosurgery.

Endocrine failure is a problem in a staged operation. If acute adrenal insufficiency, hypothyroidism and diabetes insipidus occur during the perioperative period of cardiac surgery, it might worsen the angina pectoris.[1 2] For example, administration of vasopressin induces coronary vasoconstriction. It is, therefore, important to perform cardiac surgery before any uncontrollable endocrine failure occurs. This is one of the reasons why we performed the neurosurgery before the cardiac surgery.

In conclusion, we managed a patient with severe angina pectoris and pituitary apoplexy. We have described a two staged operation with sequential management of intra-cranial haemorrhage and open-heart surgery requiring anticoagulant therapy. Our case illustrates the importance of coronary care during the time between the two operators.

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Sedation and general anaesthesia in children undergoing MRI and CT

Editor,—We read with interest the article of Malviya and colleagues[1] and the accompanying editorial.[2] They rightly comment that patients receiving nurse-led sedation or general anaesthesia were not strictly comparable as assignment to one or other group was not random. However, it is impressive that the group that received general anaesthesia was less likely to have failed or inadequate sedation and the complication rate was less, despite containing a greater proportion of ASA III and IV patients. The mean recovery time of the GA group was, however, longer than that of the sedation group. Many authors have reported the benefits of anaesthetist-administered intravenous sedation.[3–8] This approach may afford the benefits of both low failure rates and a rapid recovery.

In our hospital, all children who cannot tolerate MRI scanning awake are managed in a session providing a full anaesthetic team. The choice of technique is therefore determined by the anaesthetist rather than by the referring physician. We find that for the majority of children, anaesthetist-administered intravenous sedation has benefits over oral sedation or general anaesthesia. We administer midazolam 0.05 mg kg^{-1} and propofol 2 mg kg^{-1} i.v. over 2 min. Following this, careful assessment is made of the patency of the child's airway and adequacy of respiration during positioning of the scanner table and application of monitoring.

Sedation is maintained by intermittent administration of propofol 0.1 mg kg^{-1} min^{-1}, equivalent to 6 mg kg^{-1} h^{-1}. Patients receive oxygen via face mask and are monitored with continuous electrocardiography, pulse oximetry, capnography and intermittent non-invasive blood pressure monitoring. We have used this technique for two years (>150 patients) and found it be safe and efficient.

In their editorial, Hatch and Sury comment that it is manpower constraints that prevent many institutions from providing general anaesthesia rather than sedation, which they later note is 'at best time consuming and at worst unreliable'. In hospitals with a smaller workload of paediatric MRI, such constraints may not exist as the demand may be met by one or two anaesthetic sessions. In addition, in this setting of a decreased workload, it may be more difficult to maintain high standards of nurse administered sedation.

We would caution the extrapolation of the practice of large dedicated paediatric hospitals to units, in which intravenous sedation by an anaesthetist may provide a safe, reliable and efficient alternative.

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Editor,—We thank Drs Sutherland and Platt for their interest in our study. We would like to clarify that it was not feasible to make the groups strictly comparable because children were pre-selected for general anaesthesia based on a perceived increased risk from sedation due to the underlying medical history or risk of sedation failure. Randomization of these children to receive sedation may have placed them at risk for an adverse event. We agree that the use of propofol with the patient breathing spontaneously may have shortened recovery times However, it could be argued that the use of a potent respiratory depressant such as propofol in the absence of a secure airway and controlled ventilation, in a situation that allows little to no immediate access to the patient, may present an undue risk of hypoxaemia and hypoventilation. Several reports in the literature attest to the safety of propofol in spontaneously breathing patients undergoing MRI scans.[1–4] The majority of these reports, however, have studied small numbers of patients and generalization of the results is confounded by differences in patient selection, varying doses of propofol used, and inconsistent compliance with mandated standards for monitoring of sedated and/or anaesthetized patients.[5 6] Data from a large prospective study that demonstrates the safety of this anaesthetic technique are required before its routine use can be recommended for MRI scanning.

The editorial by Hatch and Sury[7] compares our incidence of adverse events unfavourably with their own series.[8 9] Yet, they report a 5% incidence of unsuccessful scans, 3% incidence of supplemental oxygen requirements and 1% incidence of oxygen desaturation, which is not significantly different from our findings. Unlike the study of Sury and colleagues, our studies have included inadequate sedation in our incidence of adverse events because it affects the quality and duration of the scans. It remains difficult to compare the incidence of adverse events reported in different studies due to variability in the definition of adverse events, and in the methods of data collection and reporting.

Provision of high quality and safe sedation care to children undergoing MRI scans continues to pose a challenge. Indeed in some centres like that of Sutherland, this challenge is met by provision of deep sedation or general anaesthesia by anaesthetists. We have demonstrated that general anaesthesia provides a suitable alternative to sedation administered by non-anaesthetists without adding risk while eliminating the potential for failed sedation. In most settings, cost and personnel constraints limit the availability of anaesthesia teams such that sedation of children remains in the realm of non-anaesthetists. Continuous quality improvement processes, therefore, remain imperative to assure the safety of sedated children. Indeed, the results of our studies have led to

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revision of our practice of primary physicians ordering sedatives. Sedatives are now ordered by the radiologist responsible for the procedure after careful review of the child's underlying history, and in accordance with protocols developed under the guidance of anaesthetists. Unfortunately, no sedative regimen has been shown to be effective for all children. Evaluation of sedative regimens that are reliable, yet have a sufficient margin of safety, remains open to further investigation.

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Low-flow definition, concentration and cost of anaesthetics

Editor,—In the literature, there are several recommendations of gas flows[1–4] for low-flow anaesthesia; Meakin[4] suggests another one with a 'flow rate less than the patient's alveolar ventilation'. However, he does not specify how much less the inflow of gases should be.

Based on the concept that intravenous anaesthetics are given to patients in relationship to body weight (mg kg^{-1}), Couto da Silva and Aldrete[5] proposed a classification of anaesthetic gas flows based on a ml kg^{-1} basis.

The metabolic consumption of oxygen (ml) per minute may be calculated by Brody's[6] equation 10 × body weight in kg$^{3/4}$; so, a 70 kg patient will consume about 242 ml min^{-1}. Since this is the inflow rate recommended for use in closed circuit anaesthesia,[6] Couto da Silva and Aldrete[5] suggested that the equation 10 × body weight in kg$^{3/4}$ should be multiplied by an arbitrary factor of 2.5 for their classification; they considered 25 × body weight in kg$^{3/4}$ as the highest acceptable limit total of gas flow (O_2, N_2O and anaesthetic vapours) when employing closed systems and the lowest one for low flow. The highest limit of low flow would be obtained in the same way (25 × body weight in kg$^{3/4}$ × 2.5 = 62.5) but for simplicity's sake it was considered as 60 × body weight in kg$^{3/4}$; this would also be the lowest limit of intermediate flow. High flow would be employed with flow rates above 150 kg$^{3/4}$ (60 × body weight in kg$^{3/4}$ × 2.5).

Meakin[4] measured the fresh gas inflow in children aged 1 month–16 yr and kept a maintenance flow of 0.8 litre min^{-1}; he does not present the mean age or the mean weight of these patients but the 1 month baby certainly received a higher inflow of gases than that he had proposed. In comparison with our proposal,[5] it is possible to state that in all the children weighing less than 10 kg, Meakin[4] used intermediate or high flows of gases instead of low flow.

I would like to emphasize the difficulty in obtaining an adequate anaesthetic concentration with the vapourizer outside the circuit (Mapleson A) with flow rates below 1 litre min^{-1}; this is true especially in underdeveloped countries, where a reliable vapourizer is difficult to acquire.

Finally, I agree that low flow and especially closed system anaesthesia decrease costs, even in paediatric patients.[7] A newborn baby has been anaesthetized for 63 min for the treatment of imperforate anus with 0.8 ml of halothane for induction and maintenance of anaesthesia.[8]

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Editor,—In my article on low-flow anaesthesia for infants and children, I distinguished between three fresh gas flows for use with anaesthetic breathing systems: high flow–any flow rate greater than the patient's alveolar ventilation; low flow–any flow less than the patient's alveolar ventilation; and closed system anaesthesia–the use of a flow rate just sufficient to replace the volume of gas and vapour taken up by the patient.[1] My intention, and I apologize if this was not clear, was to suggest that the basal flow for closed system anaesthesia should be regarded as the lower limit of low flow anaesthesia. This is similar to a proposal by Couto da Silva and Aldrete;[2] however, the definition of closed system flow proposed by these authors, a range up to 2.5× basal oxygen flow, would appear to be somewhat arbitrary when compared with the generally accepted definition cited above. The same can be said of the definition of intermediate flow which was considered to be 6× the basal oxygen flow.

Although the definition of low flow anaesthesia I have proposed is theoretically sound, it may be impractical to apply it to the youngest patients because of their small alveolar ventilation requirements. For example, in the 1 month-old infant referred to by the correspondent (body weight 3.2 kg), the calculated basal oxygen consumption was 24 ml min^{-1} and normal alveolar ventilation 384 ml min^{-1}. Applying the formulae given in my review, the flowmeter settings required to ensure an $F_{I_{O_2}}$ of 0.33 with this flow rate during nitrous oxide–oxygen anaesthesia would be 132 ml min^{-1} O_2 and 252 ml min^{-1} N_2O. Clearly, the oxygen flow rate would be difficult to deliver accurately from flowmeters calibrated to the nearest 50 ml min^{-1}, and impossible to deliver if the flowmeters were set, as is customary, to deliver a minimum of 250 ml min^{-1} of oxygen. For this reason, the maintenance flow used in our economics study was 0.8 litre min^{-1},[3] while in the review I calculated fresh gas flow settings to provide an $F_{I_{O_2}}$ of 0.33 during low flow anaesthesia in infants, children and adolescents with maintenance flow rates of 0.6 and 1.0 litre min^{-1} (Table 1) [1]

Table 1 Oxygen (O_2) and nitrous oxide (N_2O) flowmeter settings for use with low flow anaesthesia in paediatric patients The flowmeter settings were calculated to provide an $F_{I_{O_2}}$ of 0 33 with total fresh gas flows ($\dot{V}_F$) of 1000 ml min^{-1} or 600 ml min^{-1}, based on the upper limit of each weight range Percentage oxygen concentration is provided for use with machines fitted with fresh gas mixing valves. All values are approximate

Age group	**Wt (kg)**	**Flow meter settings for $\dot{V}_F$ 1000 ml min^{-1}**			**Flowmeter settings for $\dot{V}_F$ 600 ml min^{-1}**		
		O_2	**N_2O**	**O_2 (%)**	**O_2**	**N_2O**	**O_2 (%)**
Infants (<1 yr)	3–10	400	600	40	250	350	40
Children (1–12 yr)	11–40	450	550	45	300	300	50
Adolescents (>12 yr)	41–70	500	500	50	350	250	60

It is true that the output of earlier types of plenum vapourizer, such as the TEC 2 (Datex-Ohmeda Ltd, Hatfield, UK), was unreliable at low flow rates However, with modern vapourizers such as the TEC 3 and above and the Drager Vapor series (Drägerwerk, Lübeck, Germany) this problem has been virtually eliminated.[4] Nowadays, the safety of low flow anaesthesia probably owes more to the availability of multigas analysers, which permit precise control of the inspired anaesthetic concentration.

My approach to low flow anaesthesia in paediatric patients is consistent with the practice of Foldes and colleagues, who coined the phrase to describe a technique in which the maintenance fresh gas flow was reduced to 1.0 litre min^{-1} in adults.[5 6] These authors considered that the use of flow rates closer to the basal value did not confer significant advantages when compared with the use of low flow, while it increased the complexity of the conduct of anaesthesia and predisposed to equipment failure and human error. It is apparent from the example given above that such considerations apply even more when anaesthetizing small infants, and I would be reluctant to follow the example of Couto da Silva and colleagues by employing the closed system technique in a newborn.[7]

Owing to a typographical error, columns 4 and 7 of Table 2 of my review were mistakenly labelled Air and not N_2O as intended. The correctly labelled table is shown above (Table 1).

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Opioids and ventilatory timing

Editor,—Smart and co-workers conclude that breath interval gives a measure of the time course of effect of opioids.[1] Their descriptions and analyses of the effects of fentanyl on breath interval were similar to our earlier descriptions of the effects of alfentanil on expiratory time, after which we concluded that 'In the absence of other factors, expiratory time could probably be used as a measure of the effect of any opioid 7...'[2]

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Tramadol or ketamine for caudal analgesia?

Editor,—'All research should be ethical, and all investigators have an obligation to uphold the highest standards when conducting studies.'[1] Two articles published recently in the same issue of this journal, reported on studies which seem superfluous and ethically questionable. Murthy and colleagues examined the pharmacokinetics of tramadol after caudal and i.v. administration[2] and Marhofer and colleagues investigated the use of s-ketamine for caudal block.[3] Both studies were carried out in children, and this is the point of our criticism.

In the former study, five children aged 5–12 yr were given a caudal injection of tramadol for postoperative pain therapy after hypospadias repair,[2] a very similar study to an earlier one by the same authors.[4] The authors conclude that 'there is no logical reason to inject tramadol into the epidural space', since the latter serves merely as a depot for systemic absorption [2] This is the same conclusion reached 3 yr ago.[4] The authors give a conclusion long since known. Grace and colleagues, for example, discontinued their study as the pain reduction proved to be poor compared with that of morphine [5] Epidurally administered tramadol requires the same dosage and produces the same side-effects as when administered intravenously.[6] The ineffectivity and possible hazards of caudal tramadol have been commented on.[7]

The second study by Marhofer and colleagues examined the use of epidural ketamine in children.[3] Since the analgesic mechanisms of ketamine continue to be the subject of controversy, and since ketamine is not commonly used to treat postoperative pain, but rather to prevent the so-called 'wind up' phenomenon and to treat neuropathic pain,[8] it is difficult to understand why this substance would be used for this indication for children. Postoperative pain relief with epidural or intrathecal ketamine has also been studied before. Adequate analgesia could only be achieved – if at all – with a very high dosage.[8] Hawskworth and Serpell were forced to terminate their study of intrathecal use of ketamine after 10 patients due to the high incidence of side-effects and inadequate analgesia.[9] Considering the probable pharmacological mechanisms, the use of ketamine in postoperative analgesia is not logical. Local anaesthetics would most likely prove more effective.

Moreover, spinal neurotoxicity of racemic ketamine solution has been demonstrated.[10] The causes of neurotoxicity, however, continue to be the subject of controversy. Some authors blame preservatives such as benzethonium chloride or chlorbutanol for the neurotoxic effects.[11] However, despite numerous neurotoxicity studies, there are still no conclusive findings regarding its cause; s-ketamine cannot therefore be considered a safe agent to apply epidurally; and an additional risk of dose dependency provides a further complication.[8] It is for this reason that this substance is not registered for epidural use.

The Declaration of Helsinki states that in 'biomedical research the importance of the objective' has to be in 'proportion to the inherent risk to the subject'. It goes on to affirm that 'potential benefits' of a new method must 'be weighed against the advantage of the best current therapeutic methods'.[12] In the two studies in question, these basic principles have not been observed. Both studies deal with substances which are not authorized for the application studied – not even in adults, let alone children. The study objective is poor; there are a wide variety of methods and substances available for postoperative analgesia in minor surgery. The use of bupivacaine for caudal block in children has been acknowledged as providing sufficient postoperative analgesia. If local anaesthetics do not suffice, morphine, sufentanil or clonidine are well-established agents to apply epidurally. As well as caudal block, other techniques such as penile block or field block can be used.

The question therefore has to be asked in both cases: in the absence of a useful study design, was it necessary to risk harm to young children in applying epidurally a substance not registered for this use and already known to be either ineffective or potentially neurotoxic? Or could the same questions not be answered by an investigation in adults? In our opinion, the ethics of both studies are at best questionable. 'Studies which have been approved by a Research Ethics Committee (REC) may still be considered unacceptable for ethical reasons, because the REC's requirements are, in the opinion of the journal's editorial team, too lax.'[1] This is in accordance with the World Medical Association, which states that 'reports of experimentation not in accordance with the principles laid down in this Declaration [of Helsinki] should not be accepted for publication.[12] Neither study could contribute significantly to the progress of anaesthesia, even if performed on adults. Surely there is even less reason to perform these studies on young children, where ethical criteria are stronger.

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Germany

1 Editorial. Investigators, Anaesthesia and Ethics. *Anaesthesia* 2000; **55**: 521–2
2 Murthy BVS, Pandya KS, Booker PD, Murray A, Lintz W, Terlinden R Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration. *Br J Anaesth* 2000; **84**: 346–9
3 Marhofer P, Krenn CG, Pochl W, Wallner T, Glaser C, Koinig H, Fleischmann E, Höchtl A, Semsroth M. S(+)-Ketamine for caudal block in paediatric anaesthesia. *Br J Anaesth* 2000; **84**. 341–5
4 Prosser DP, Davies A, Booker PD, Murray A Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery. *Br J Anaesth* 1997; **79**: 293–6
5 Grace D, Fee JP. Ineffective analgesia after extradural tramadol hydrochloride in patients undergoing total knee replacement. *Anaesthesia* 1995; **50**: 555–8
6 Delilkan AE, Vijayan R. Epidural tramadol for postoperative pain relief *Anaesthesia* 1993; **48**: 328–31
7 Russell W. Caudal tramadol for postoperative analgesia in hypospadias surgery *Br J Anaesth* 1998; **80**. 408–9
8 Gebhardt B. Epidural and intrathecal administration of ketamine – pharmacology and clinical results. *Anaesthetist* 1994; **43**: S34–40
9 Hawksworth C, Serpell M. Intrathecal anesthesia with ketamine *Reg Anesth Pain Med* 1998; **23**: 283–8
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12 The 18th World Medical Assembly. Declaration of Helsinki. Finland June 1864, amended (Tokyo) 1975 until (Somerset West) 1996 http://www.wma.net/e/17-c_eprargraphnumbering.html

Editor,—Thank you for the opportunity to respond to the criticisms made of our study by Zenz and Zenner. Zenz and Zenner declare that we have arrived at a conclusion 'long since known'. In support of this statement they refer to a study by Grace and Fee, which was one in adults that compared morphine to tramadol, when both were given by the epidural route.[1] However, although this study found that morphine offered better analgesia than tramadol, the authors also stated that 'further study (of tramadol) may be warranted where postoperative pain is expected to be less severe ...' Moreover, their findings are in direct contrast to a previous comparative study by Baraka and colleagues, who found no significant difference in the analgesia provided by epidural morphine and epidural tramadol in adult patients having major abdominal surgery[2] Furthermore, prior to the start of our tramadol studies, we were aware of another four published studies that had examined the analgesic efficacy of epidural tramadol; all found that tramadol given by this route provided effective and useful postoperative analgesia.[3–6] Finally, just as we were starting our two tramadol studies in 1995, data were published that showed that caudal tramadol given to children undergoing hypospadias repair produced excellent long-lasting postoperative analgesia.[7] We submit, therefore, that there was good reason to suppose in 1995 that epidural tramadol was efficacious, and that it could be a useful addition to the therapeutic armamentarium currently available for paediatric day care anaesthesia.

The second point made by Zenz and Zenner regarding the ethics of conducting such research in this age group has been raised before by Russell.[8] Although it is not obvious from the difference in publication dates, this pharmacokinetic study was proceeding in parallel with the clinical study, but various protracted delays in biochemical and mathematical analysis prevented its publication until recently. Hence, we did not have the results of our pharmacokinetic study when we were conducting this clinical study (or vice versa). Hence, the ethical justification for our pharmacokinetic study[9] remains the same as that previously stated in our letter[10] to this journal following our clinical study.[11]

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1 Grace D, Fee JP. Ineffective analgesia after extradural tramadol hydrochloride in patients undergoing total knee replacement. *Anaesthesia* 1995; **50**: 555–8

2 Baraka A, Jabbour S, Ghabash M, Nader A, Khoury G, Sibai A. A comparison of epidural tramadol and epidural morphine for postoperative analgesia. *Can J Anaesth* 1993; **40**: 308–13

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5 Fu YP, Chan KH, Lee TK, Chang JC, Daly YP, Lee TY. Epidural tramadol for postoperative pain relief. *Ma Tsui Hsueh Tsa Chi* 1991, **29**: 648–52

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11 Prosser DP, Davis A, Booker PD, Murray A. Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery. *Br J Anaesth* 1997; **79**: 293–6

Editor,—Unintentional i.v. administration of bupivacaine during caudal blockage may cause serious cardiovascular and central nervous system complications.[1 2] But the administration of an epidural test dose containing epinephrine for detection of unintentional intravascular injection does not reliably produce haemodynamic responses in children during inhalation anaesthesia.[3]

Our study 'S(+)-ketamine for caudal block in paediatric anaesthesia'[4] was performed to evaluate the analgesic efficacy of 0.5 and 1.0 mg kg^{-1} caudally administered preservative-free S(+)-ketamine. We demonstrated that 1.0 mg kg^{-1} provides equi-effective intra- and postoperative analgesia compared with 0.75 ml kg^{-1} 0.25% bupivacaine plus epinephrine. In contrast to the severe cardiovascular and central nervous system complications of unintentional intravascular administration of bupivacaine, unintentional i.v. administration of S(+)-ketamine would be harmless.

We agree with Zenz and Zenner that possible spinal neurotoxicity of S(+)-ketamine is controversial. Nevertheless, most authors consider the preservatives chlorbothanol and benzethonium chloride as the neurotoxic substances.[5 6] But S(+)-ketamine is commercially available as a preservative-free substance, and other authors used preservative-free racemic ketamine for caudal blocks in children.[7] Most of the routinely used neuroaxial drugs have not been investigated for possible neurotoxicity (i.e. fentanyl, sufenanyl, epinephrine and most of the local anaesthetics).

S(+)-ketamine has a similar chemical structure to bupivacaine. The local anaesthetic effects are caused by NMDA receptor antagonism, opioid μ-receptor agonism and voltage-sensitive sodium channel interaction. These different mechanisms of analgesia also make this substance useful for perioperative pain therapy and a large number of *in vitro* and *in vivo* studies support this. The possibly severe complications of caudally administered bupivacaine justify studies with caudally administered S(+)-ketamine. Our results suggest that S(+)-ketamine shows neuroaxial effects, and pharmacokinetic data about blood levels of caudal versus i.m. administered S(+)-ketamine support these results.[8]

We agree with Zenz and Zenner that S(+)-ketamine should not be used for intrathecal administration at present. But by performing caudal blocks, the local anaesthetic will be administered epidurally, and not intrathecally.

Peter Marhofer
Margot Semsroth
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Austria

1 Freid EB, *et al.* Electrocardiographic and hemodynamic changes associated with unintentional intravascular injection of bupivacaine with epinephrine in infants. *Anesthesiology* 1993; **79**. 394–8

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5 Malinovsky JM, *et al.* Is ketamine or its preservative responsible for neurotoxicity in the rabbit? *Anesthesiology* 1993, **78**: 109–15

6 Migaly P. The problem of intrathecal ketamine *Br J Anaesth* 1986; **58**: 684

7 Naguib M, *et al.* Ketamine for caudal analgesia in children. comparison with caudal bupivacaine. *Br J Anaesth* 1991; **67**· 559–64

8 Koinig ?, *et al* Analgesic effects of caudal and intramuscular S(+)-ketamine in children. *Anesthesiology* 2000; in press

Acupressure and prevention of nausea and vomiting

Editor,—I read with interest Dr Harman and colleagues' paper about a non-pharmacological technique to reduce nausea and vomiting during spinal anaesthesia for Caesarean section.[1] These symptoms are unpleasant and are effects patients would most like to avoid.[2] The investigators' choice of intrathecal drugs may be affecting the incidence of intraoperative nausea and the need for intravenous opiates to supplement spinal anaesthesia. The onset time for analgesia with intrathecal fentanyl is less than 10 min in comparison to 60–120 min for intrathecal morphine.[3] Intrathecal fentanyl will improve analgesia during a Caesarean section under spinal anaesthesia and reduce the incidence of nausea and vomiting during the operation.[4] Some have even suggested intrathecal fentanyl is as effective an antiemetic as intravenous ondansetron in this clinical setting.[5]

The optimization of intrathecal medication should be considered in synchrony with any additional intervention to reduce the incidence of nausea during a Caesarean section.

Paul J Youngs
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1 Harmon D, Ryan M, Kelly A, Bowen M. Acupressure and prevention of nausea and vomiting during and after spinal anaesthesia for Caesarean section. *Br J Anaesth* 2000, **84**: 463–7

2 Macario A, Weinger M, Carney S, Kim A Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg* 1999, **89**: 652–8

3 Hamber EA, Viscomi CM. Intrathecal lipophilic opioids as adjuncts to surgical spinal anesthesia. *Reg Anesth Pain Med* 1999; **24**: 255–63

4 Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA. Does intrathecal fentanyl produce acute cross-tolerance to i.v morphine? *Br J Anaesth* 1997; **78**· 311–3

5 Manullang T, Viscomi CM, Pace NL. Intrathecal fentanyl is as effective as intravenous ondansetron for the prevention of intraoperative

nausea during Cesarean section under spinal anesthesia. *Anesthesiology* 1999; SOAP abstracts: A52

Editor,—We would like to thank Dr Young for his interest in our paper regarding the use of acupressure in prevention of nausea and vomiting associated with Caesarean section under spinal anaesthesia including intrathecal morphine. He makes a valid point regarding choice of intrathecal opiate and the incidence of nausea and vomiting.

Intrathecal fentanyl has a faster onset but a shorter duration of action than intrathecal morphine limiting its effectiveness for postoperative analgesia.[1] Its recent description as a method to reduce nausea and vomiting[2] is interesting. Nausea and vomiting associated with intrathecal morphine appears to be dose-dependent.[3] The 0.2 mg dose used in this study could explain the high incidence of nausea and vomiting in the control group. We have changed our practice in the light of this study and now use a lower dose of intrathecal morphine.

As described in our paper, intrathecal morphine was chosen for the quality of postoperative analgesia[4] not found with intrathecal fentanyl. With intrathecal fentanyl, the poorer postoperative pain control and increased systemic opiate requirement would likely increase the incidence of postoperative nausea and vomiting. Nausea and vomiting in the intra-operative and postoperative periods is a significant problem in this setting and must be considered in the choice of anaesthetic technique. If intrathecal fentanyl could be demonstrated to reduce postoperative nausea and vomiting it might change our practice. Intrathecal morphine at a lower dose would remain our technique of choice for the reasons outlined.

Dominic Harmon
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1 Dahlgren G, Hulstrand C, Jakobson J, Norman M, Erickson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for Cesarean section. *Anesth Analg* 1997; **85**: 1288–93
2 Milner AR, Bogod DG, Harwood RJ. Intrathecal administration of morphine for Cesarean section. A comparison between 0.1 mg and 0.2 mg. *Anaesthesia* 1996; **51**: 871–3
3 Manullang TR, Viscomi CM, Pace NL. Intrathecal fentanyl is superior to intravenous ondansetron for the prevention of perioperative nausea during Cesarean delivery with spinal anesthesia. *Anesth Analg* 2000; **90**: 1162–6
4 Abouleish E, Rawal N, Fallon K, Hernandez D. Combined intrathecal morphine and bupivacaine for Cesarean section. *Anesth Analg* 1988; **67**: 370–4

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Book Reviews

Pharmacology for Anaesthesia and Intensive Care T.E. Peck and M. Williams. Published by Greenwich Medical Media. Pp. 256; illustrated. Price £24.50. ISBN 184 1100250.

The authors state in their preface that this book has been written to help people prepare for the FRCA, especially the primary examination. It has also been written for physicians looking after the critically ill who are not anaesthetists, and for others caring for patients in the operating theatre and the intensive care unit who want to understand drugs better.

To achieve this, the book is divided into four sections: basic principles; core drugs in anaesthetic practice; cardiovascular drugs; and other important drugs. Also included with the book is a CD ROM containing multiple choice questions.

The first section contains chapters on drug passage across the cell membrane, absorption, distribution, metabolism and excretion, drug action, drug interaction, isomerism, and finally, mathematics pharmacokinetics. I enjoyed reading this section and found it clear and well presented. In the section on metabolism, I would have liked to have seen some expansion of the description of the cytochromes P450 and other enzymes since an understanding of this area allows drug interaction to be more readily predicted and appreciated.

Section two contains the core drugs used in anaesthesia and has chapters on intravenous and inhaled anaesthetic agents, analgesics, local anaesthetics and muscle relaxants. All of the important drugs are mentioned in this section along with good descriptions of their mechanisms of action. My only criticism is that the chapter on neuromuscular blocking drugs does not adequately describe monitoring. For example, knowledge of train of four responses and post-tetanic facilitation is assumed rather than explained. In contrast, the section on succinylcholine I found well described and useful.

Section three considers the cardiovascular drugs, including sympathomimetics, adrenoreceptor antagonists, anti-arrhythmics, vasodilators and anti-hypertensive drugs. Again, there were clear descriptions of the drugs.

Section four I found rather disappointing. Here are described the benzodiazepines and anti-microbials. The description, particularly of the latter, is far too brief for a book describing pharmacology for treatment of the critically ill. Similarly, the description of insulin I would have liked to have seen in a little more detail.

In most text books there are small errors. This book is no exception and contains several. For example, in the chapter on neuromuscular blocking drugs, the authors state that myopathy has been reported following administration for prolonged periods of the steroid-based relaxants. This is true, but it has also been reported with other relaxants. When discussing midazolam, the authors state that it has no active metabolites. This phase one metabolite does have activity and, more importantly, the phase two metabolite is retained in renal failure and is a cause of coma. When discussing the benzodiazapine antagonist, flumazenil, the authors fail to mention that it should not be given to patients with mixed drug overdoses because of the risk of producing fits.

The CD ROM loads easily and, once opened, you can create your own examination, or 'sit' one of six preset ones. Each examination contains 25 questions with five parts. They an be answered as yes, no, or don't know. The marking for each examination includes negative marking. When opening an examination, you can choose to monitor your level of confidence in the answers. This allows you to see whether a guessing strategy works or not!

Despite my criticisms, I do feel that this is a useful, easy to read, and informative text book. Although it is heavily biased towards anaesthesia rather than intensive care, it will be of great value to three groups for whom it is intended. At £24.50, including the CD ROM, it also represents good value for money.

G. R. Park
Cambridge

Pain Procedures in Clinical Practice, Second Edition. Lennard (editor). Published by Hanley & Belfus, Philadelphia. Pp. 434; indexed; illustrated. Price £55. ISBN 2-56053-367-6.

As the title implies, this text aims to provide information about technical procedures for clinicians in pain management. Almost 50 contributors, all but one from the USA, give the book a distinctly North American flavour. Pain management is a widely multidisciplinary and multiprofessional specialty and this text is clearly aimed at an audience much wider than those with a background in anaesthesia. For example, the recommendations on treatment of adverse reactions reflects this suggesting that toxic convulsions are treated with oxygen, airway management, and diazepam followed by hospitalization and appropriate consultation. One of the problems I found was the breadth of material it attempted to cover. In a text of this length the inevitable consequence is that many areas are covered superficially. The discussion of the use of neurolytic agents is confined to phenol and even this is rather limited. The suggestion that phenol should be avoided in patients with significant liver disease because it is eliminated through the liver will surprise many who find it useful for intercostal nerve block for rib metastases and other similar procedures in palliative care.

The book includes chapters on the management of wounds and chronic ulceration, swallowing videofluoroscopy, urodynamics, serial casting, medical acupuncture, prolotherapy and cervical discography, in addition to the description of numerous nerve blocks and their application. I doubt that many pain specialists in the UK would consider the investigation of swallowing or urological problems part of their clinical practice although this may not be the case in the USA. Acupuncture is not merely a procedure or even a collection of procedures and ten pages can do little more than provide a very basic outline. Another example of the transatlantic difference in practice concerns the use of coeliac plexus block. In the UK, most pain management clinicians would regard the principal indication for this as the treatment of malignant pain. Therapeutic (and by implication, diagnostic) block with local anaesthetic agents and the use of methylprednisolone for acute pancreatitis are mentioned here but with no real discussion and nothing about malignant pain.

The descriptions of nerve blocks, which are accompanied by monochrome illustrations, are reasonably good but not of as high a standard as some of the excellently written and illustrated texts on regional anaesthetic techniques. The most disappointing feature in a text such as this, however, is the paucity of detail on when to use, how best to use and most importantly when not to use each block. This is really treated very superficially. Often there is little or no more than a list of conditions with no discussion of when a block is appropriate or the circumstances under which local anaesthetic agents or radiofrequency lesioning would be preferred.

I doubt if this text will prove particularly relevant for clinicians in pain management in the UK. It certainly is not suitable for trainees studying for the FRCA and could not be recommended even for trainees pursuing an interest in pain management. It may find a place in some libraries in pain management centres where an impression of the very different nature and scope of this subspecialty on the other side of the Atlantic would be of interest.

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Erratum

Fentanyl protects the heart against ischaemic injury via opioid receptors, adenosine A_1 receptors and K_{ATP} channel linked machanisms in rats (BJA 2000; 84: 204–14)

Fentanyl reduces infarction but not stunning via δ-opioid receptors and protein kinase C in rats (BJA 2000; 84: 608–614)

After a recalculation, the authors discovered that the concentration of fentanyl in the perfusate was 470 nmol $litre^{-1}$ rather than 740 nmol $litre^{-1}$ as quoted in the text (page 204, summary, line 5; page 205, right column, line 38; page 212, left column, line 44; page 608, summary, line 5; page 609, right column, line 20).

The authors apologize for this error.

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2 Hull CJ. Opioid infusions for the management of postoperative pain In. Smith G, Covino BG, eds. *Acute Pain.* London: Butterworths, 1985; 155–79

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3. Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois: Charles C. Thomas, 1979

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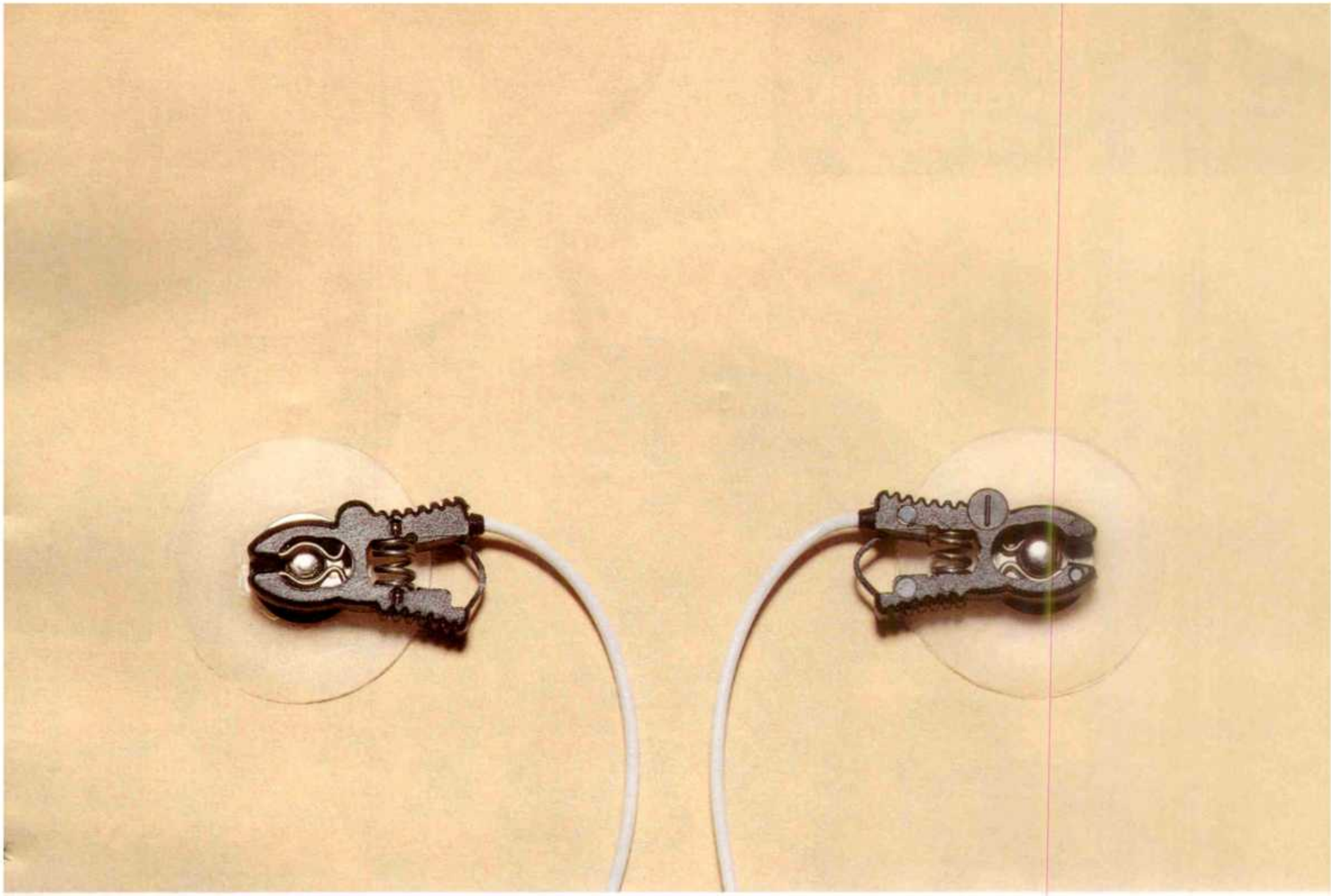

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PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib. Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

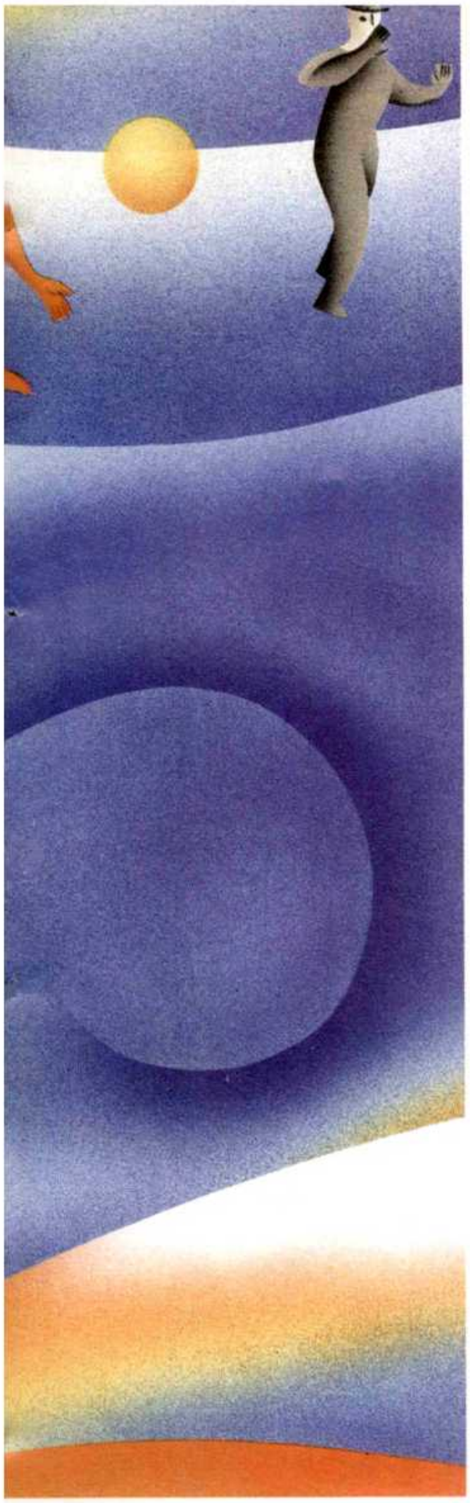
Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib. Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



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rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

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Marketing Authorisation holder

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** May 2000.

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References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Langman MJ, Jensen DM, Watson DJ et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;282(20):1929-1933.

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05-01 VOX 00 GB 65260 Jc

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK. (PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.

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References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

Please see abbreviated Prescribing Information on adjacent page.

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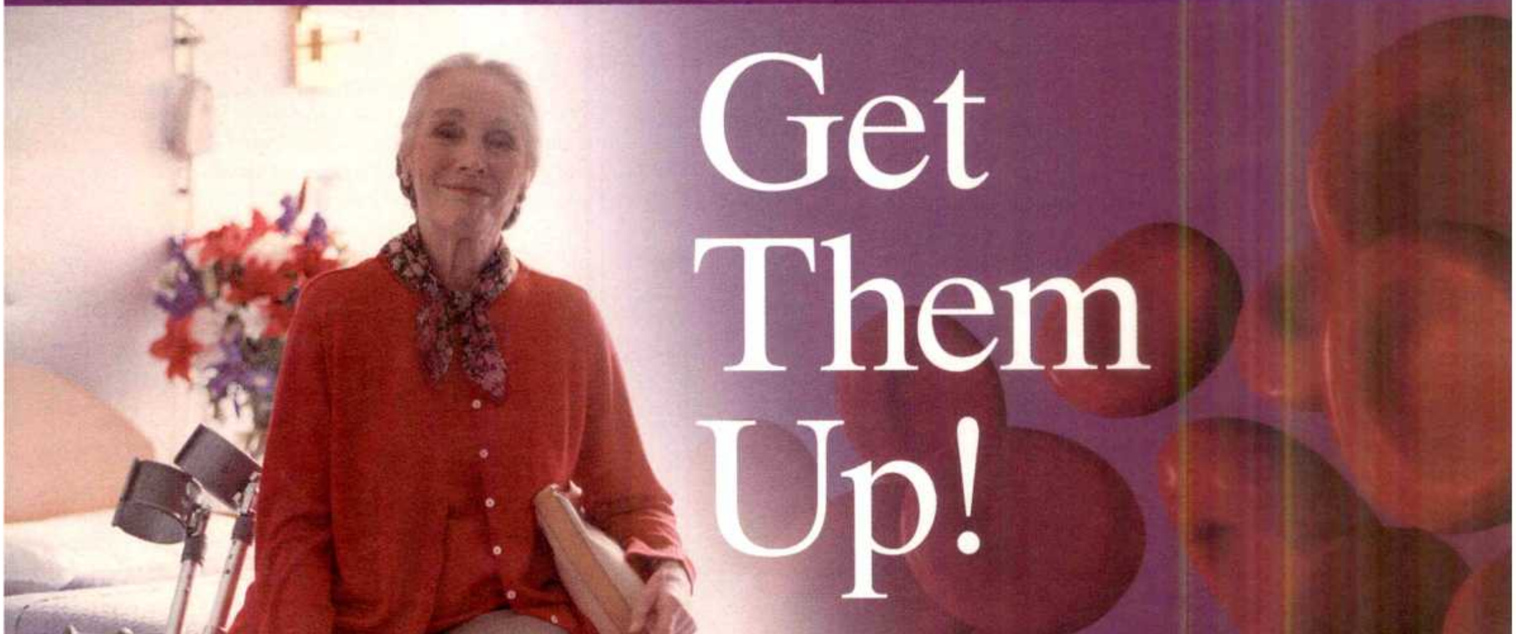

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Fax: (412) 648-1887
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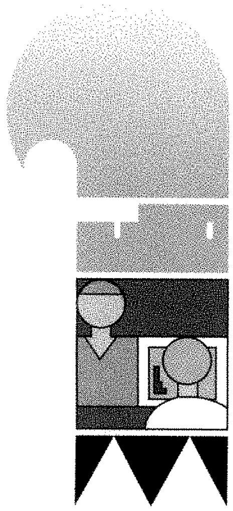

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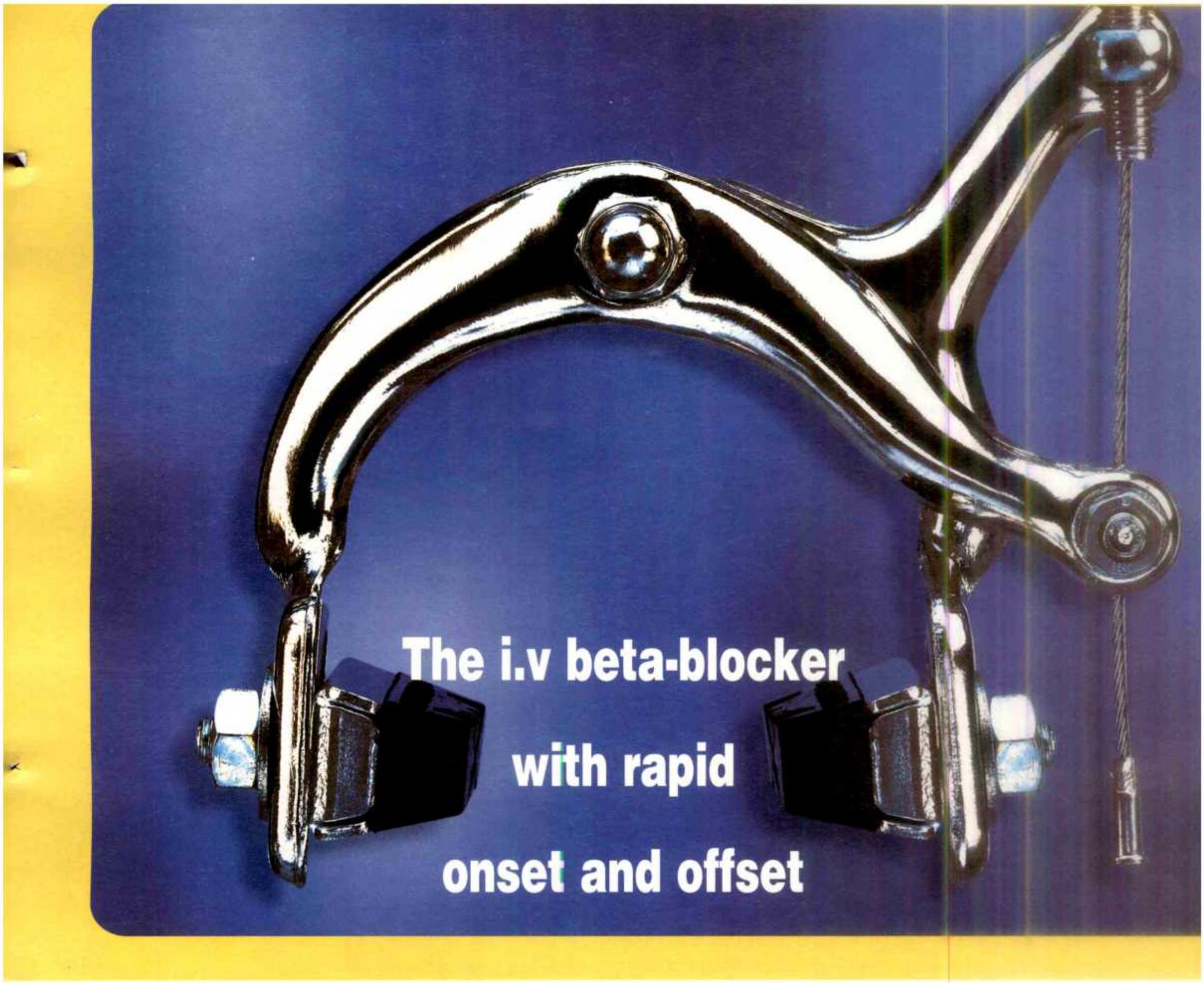

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Editorial Notices

Royal Medical Benevolent Fund

The Royal Medical Benevolent Fund reminds readers of its Christmas Appeal. Your generosity last Christmas enabled the Fund to distribute additional seasonal support of £75 000 to help bring some semblance of happiness and dignity to those doctors, and particularly their bereaved families, less fortunate than us. Each year our general grants total over £800 000. The fund always seeks to give this extra help at Christmas with gifts to the children involved.

Contributions marked 'Christmas Appeal' may be sent to the Chief Executive Officer of the RMBF at 24 King's Road, Wimbledon, London SW19 8QN or to the Treasurer of your local guild of this Fund. (Cheques payable to RMB Fund.)

BJA/RCA Research Grants

The *British Journal of Anaesthesia*, in conjunction with the *Royal College of Anaesthetists* is making a further round of grants available to support research in anaesthesia, intensive care or pain relief. The work must be conducted in the United Kingdom.

Grants are available to support specific projects in anaesthetic departments. Joint applications with basic science departments will be welcome. These grants may be awarded to fund technical staff, research students or post-doctoral research fellows: salaries, or items of equipment. The maximum value of any award will be £50 000, and the *BJA/RCA* will not contribute towards overheads.

The *BJA/RCA* will not be funding Research Fellowships with this round of awards. Applicants should note that candidates will usually be established members of academic departments of Anaesthesia in the United Kingdom; and the grant must be administered by an academic department of Anaesthesia and have the support of the Head of that Department.

For further details and forms, please **WRITE** or **e-mail** to:

Dr J. W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Headington, OXFORD OX3 9DU *or*
john.sear@nda.ox.ac.uk

Closing date for applications is **January 19th 2001**. Late applications will **not** be considered.

Combined Scientific Meeting (CSM 2001) of The Australian and New Zealand College of Anaesthetists (Faculty of Intensive Care and Faculty of Pain Medicine) and The Hong Kong College of Anaesthesiologists

Hong Kong Convention and Exhibition Centre, Hong Kong, May 5–9, 2001

Abstracts deadline: November 5, 2000

For further information please contact: CSM 2001 Hong Kong Conference Secretariat, International Conference Consultants Ltd, Unit A, 3/F Eton Building, 288 Des Voeux Road Central, Hong Kong. Tel: +852 2559 9973; Fax: +852 2547 9528; E-mail for abstract submission: CSM2001 abstract@icc.com.hk; E-mail for general enquiries: CSM2001@icc.com.hk; Website: www.CSM2001.com

5th International Conference on Memory, Awareness and Consciousness – Pharmacology and Impact on Surgical and Critically Ill Patients

New York City, USA, June 1–3, 2001

This conference builds on the tradition of the previous Memory and Awareness in Anesthesia Conferences, and will focus on the following topics: measurement and monitoring of memory function, awareness and consciousness; interaction of anesthetic and sedative drugs with the mechanisms of consciousness, awareness and memory processes; consequences and treatment of unwanted awareness or memory function during surgery or critical care; impact of surgery, anesthesia and critical care on cognitive and psychological processes; neuroimaging and mapping of consciousness, memory, awareness and pharmacologic effects on them in the CNS.

Deadline for abstracts: December 10, 2000.

For further information contact us via e-mail at mac@mskcc.org or visit our web site www.maacc.org or by mail: Ruth Reinsel, PhD, Dept of Anesthesiology/CCM, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10021, USA.

Tel: +1 212 639 6038; Fax: +1 212 772 8646.

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

Free Papers will be accepted for oral and poster presentation in four categories: (i) monitoring; (ii) new pharmacological agents; (iii) interesting case reports; (iv) cardiopulmonary bypass technology. Abstracts forms are available upon request. The deadline for submission is November 1, 2000. Tuition will not be waived. Brochure available in June 2000.

For information and abstract forms contact: Helen Phillips,

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Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

Association of Cardiothoracic Anaesthetists

Symposium on Cardiopulmonary Transplantation
Newcastle upon Tyne, UK, February 1, 2001

Topics include: (i) Management of end-stage respiratory failure; (ii) Mechanical support for the failing heart; (iii) Cardiac transplantation; (iv) Cardiopulmonary transplantation in children; and (v) Re-perfusion injury.

For further information and registration details please contact: Dr S. R. Haynes, Department of Cardiothoracic Anaesthesia, Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN, UK.

Tel: +44 (0) 191 2843111, ext: 26488; Fax: +44 (0) 191 2231175; E-mail: judith.iley@nuth.northy.nhs.uk

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)
Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

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16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail: akabogu@mcn-nuernberg.de; www: http://www.mcn-nuernberg.de

Third European Congress of Orthopaedic Anaesthesia 2001

Royal Lancaster Hotel, London, England, May 31–June 2, 2001

Information: Prestige Promotions 107 High Street, Berkhampstead, Herts HP4 2DG.
Tel: 01442 879000. Fax: 01442 870999.
E-mail: enquiries@prestige-promotions.co.uk

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

26th Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Tromsø, Norway, June 13–17, 2001

For further information please contact: SSAI Scientific Secretariat, Department of Anaesthesiology, University Hospital, N-9038 Tromsø, Norway.

Tel: +47 77 62 7001; Fax: +47 77 62 61 92, E-mail: SSAI.2001@rito.no
Web site: www.ssai2001.org

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact·

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

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ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

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Refresher Course in Anaesthesiology

Durban, South Africa, September 22–23, 2001

For further information contact: Congress Office. Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: mahti@med.und.ac.za Website. http://www.und.ac.za/med/anaesth/sasa2001.html

Second All Africa Anaesthesia Congress in conjunction with the National Congress of the South African Society of Anaesthesiologists

Durban, South Africa, September 23–26, 2001

For further information contact: Congress Office, Department of Anaesthesia, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa. Tel/Fax: +27 31 260 4472; E-mail: maliti@med.und.ac.za Website: http://www.und.ac.za/med/anaesth/sasa2001.html

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

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8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN-00029 HUS, Finland.

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Cancer Pain Management

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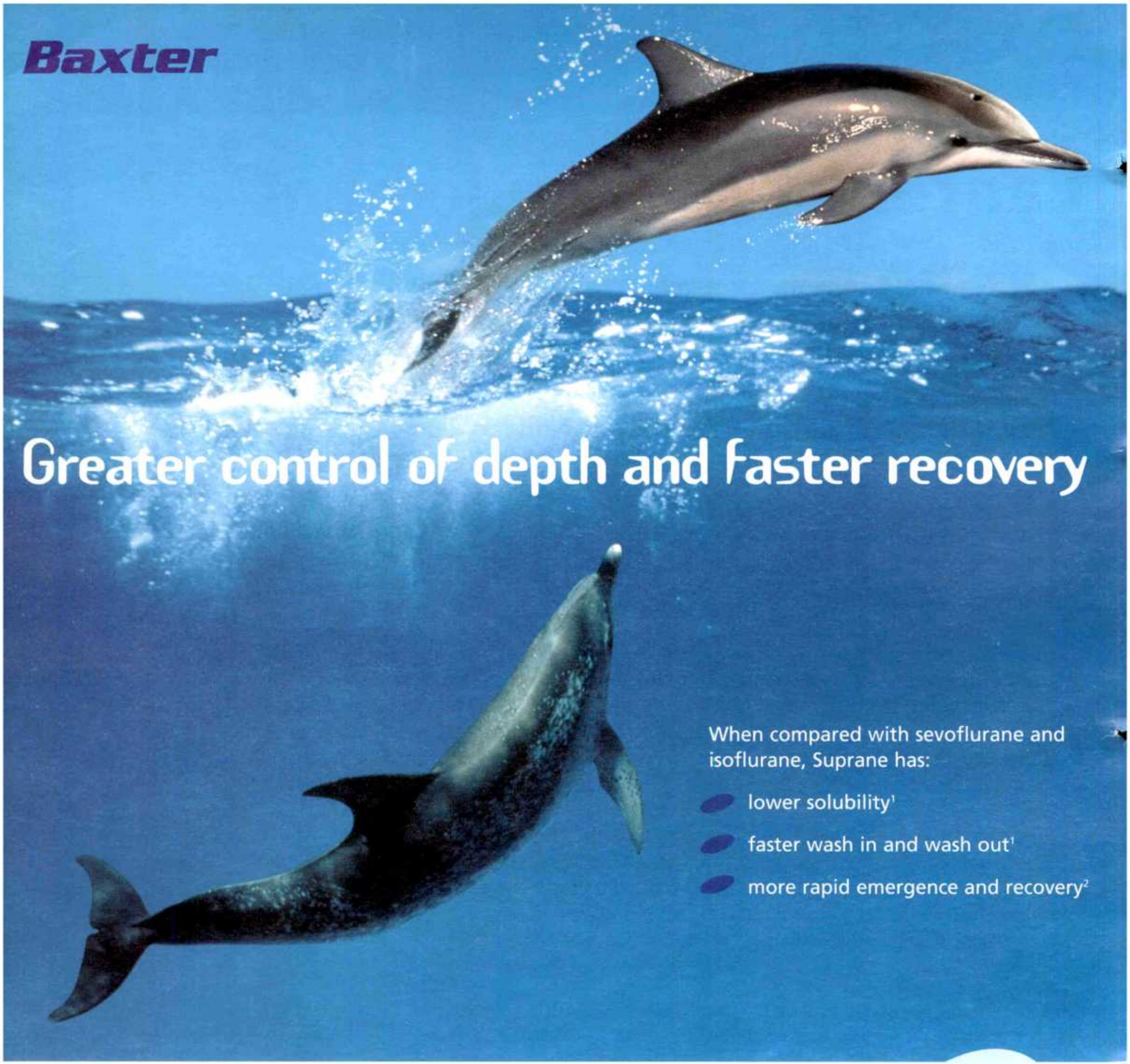
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or its competitor, or receipt of funding from the sponsor) or being an 'academic competitor' of the authors.

Responsibilities of the reader

Review articles and original scientific reports contain subjective elements and therefore offer a distorted view of reality; the only variable is the degree of distortion. Readers must adopt a critical approach to published material and be prepared to make judgements about the quality of the methodology and analysis that is presented to them.

What are the consequences for journals?

Conflicts of interest damage journals as well as authors. In 1997, the *New England Journal of Medicine* published a review[20] by Dr Gerry Berke of the book *Living Downstream: an Ecologist Looks at Cancer and the Environment*, by Sandra Steingraber. The review described the book as 'an environmental polemic', 'not. .. supported by serious scientific analysis', 'obsessed. .. with environmental pollution as the cause of cancer'. The reviewer did not reveal that he was the medical director of a chemical company that was currently under criticism for polluting drinking water and contaminating soil. The publication of this review greatly embarrassed the *New England Journal of Medicine*.

In the future, journals that are less than rigorous in identifying and addressing conflicts of interest may find themselves in litigation with aggrieved authors, companies or publishers.

Interactions with pharmaceutical companies

Commercial drug development is driven by the limited patent protection, usually 20 years, given to new molecules. Pharmaceutical companies need to refresh their portfolios with patent-protected compounds to replace the revenues lost when older drugs are lost to generic manufacturers.

For a new, and usually more expensive, drug to replace an older one, it must claim novel benefits. These claims must be supported by data. Companies therefore seek data that support their ambitions for their products. Clinical investigators advise pharmaceutical companies and test their compounds. Inevitably some of the commercial enthusiasm for a project transfers itself to the investigator.

The pharmaceutical industry is currently in rapid retreat from anaesthesia, with few compounds in development for a market which is relatively small compared with those for drugs to treat cardiovascular disease, cancer or chronic pain, and unlikely to expand. Current commercial battles (Table 1) will run on for a few years and new ones may replace them. Rather than hide these conflicts or stigmatize those who participate in them, we should campaign for greater transparency so that readers may decide for themselves.

What do other journals do at the moment?

The *British Medical Journal* has provided constant editorial innovation in biomedical publishing. In 1998, it revised its policy on conflicts of interest and now requires authors to declare 'competing interests', suggesting that authors may be concerned that admission of a 'conflict of interest' may imply 'wickedness' or that they may be so confident that they are not influenced by a conflict of interest that they do not declare it.[21]

Asai and Shingu[22] examined the instructions to authors of English language anaesthesia journals. Seven of the 11 examined during 1998 required some statement about conflict of interest; however, the extent of disclosure required is variable. *Anesthesiology* provides a comprehensive draft covering letter and lengthy conflict of interest statement which must be completed for all submitted manuscripts [23]. The *British Journal of Anaesthesia* at present manages with a single sentence (see above).

What should the British Journal of Anaesthesia do next?

The editorial board is reviewing our policy on conflict of interest. From the beginning of 2001 the Editors of the *British Journal of Anaesthesia* plan to increase the degree of disclosure required from authors and the extent to which that information is revealed to the reader. Ideally, the editors of all leading anaesthesia journals would agree a uniform approach to this matter. This may take some time!

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Editorial II

Skin testing and the anaesthetist

In 1969, Hurwitz[1] commented that the more drugs a patient receives, the greater the risk of an untoward reaction. Multiple drugs need to be used in surgery, since no single drug supplies all pharmacological needs, and this encourages unexpected drug interaction and pharmacological response. Problems are compounded by the necessity to use the intravenous route for drug administration, thus bypassing the body's primary immune filters and presenting high concentrations of noxious chemicals directly to sensitive cells, notably mast cells and basophils.[2] The substances liberated include histamine, eicosanoids and cytokines. The clinical outcome is not infrequently an immediate exaggerated systemic inflammatory response presenting hypotension and bronchospasm with varying degree of severity and which may, or may not, be immune (antibody) mediated. All such clinical presentations are usually referred to as anaphylactoid until laboratory and *in vivo* analysis can establish a genuine immediate immune-mediated hypersensitivity response (type I, IgE-mediated anaphylaxis) or otherwise, and the causative agent responsible. There are other types of drug hypersensitivity response, notably IgG (type III)-mediated response to certain clinically used dextrans and a multiplicity of responses to penicillins (potentially types I, II and III). In the majority, cause and effect is somewhat transparent and the immediate hypersensitivity response, with its requirement for immediate clinical intervention, is the greatest threat to the patient. Identification of the reaction mechanism is important both for the patient's surgical future and as defence for the anaesthetist in the increasing tide of litigation. The predominant cause of such a reaction is a neuromuscular blocking agent (NMBA) or, rarely, a hypnotic agent.[3]

While sequential analysis of plasma tryptase levels as a measure of mast cell degranulation is the most reliable marker of a drug-related event,[4] tryptase release *per se* is not a specific marker of anaphylaxis.[5,6] Anaphylaxis is a quantitative, not a qualitative, phenomenon and it becomes necessary to demonstrate not only the level of tryptase release but also the specific antibody responsible. The predominant test for the latter has been 'skin testing' against the drugs administered, with radioimmunoassays carried out either supplementary to the skin test, at autopsy or when urgent surgery is necessary before the skin test can be carried out (usually 4–6 weeks after the event). Incidentally, most of the current commercially available immunoassays employ colorimetry or fluorimetry for quantification, rather than radioactivity.

For more than two decades, the skin testing procedure has been dominated by two groups, led by Fisher and Baldo in Australia and Laxenaire and Moneret-Vautrin in France. It should be pointed out that the term 'skin testing' is widely

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used in the literature as synonymous with 'intradermal skin testing'. However dermatologists also routinely use prick testing for common allergens and this test depends largely on the presence of sensitized lymphocytes. Whereas intradermal drug tests present high concentrations of active chemicals directly to skin mast cells, indirect contact occurs with the scratch test. Although the visual endpoint of either test is the classic weal-and-flare response, the latter test should largely filter out reactions caused by non-immunological mast cell activation mechanisms.[7] In a comparative prospective study, Fisher and Bowey[8] found no statistically significant difference between the two, but a comparative trial in reactors is lacking. Ideally, both tests should be carried out on the patient[7 8]

Modern developments of NMBAs centre around two main chemical classes, the aminosteroids and the benzylisoquinolines, and these have given rise to clinically safer compounds. However, Levy and his colleagues report in this issue of the journal[9] that these drugs can induce positive weal-and-flare responses independent of mast cell degranulation and that this can confuse allergy testing and interpretation between different investigators, particularly at the test concentrations usually recommended. Although a prospective study, it does receive support from reactor studies (rocuronium) carried out by Neal and colleagues.[10] Threshold test concentrations have been described in the past, and are usually 1:1000 of ampoule concentration but as high as 1:10 for rocuronium. For the new drugs these concentrations may still be too high and the high incidence of positive cutaneous responses to rocuronium reported in France[11] may well contain a high proportion of false positives.

The major problem with all skin testing is what you see is all that you get, a weal and flare. The problem lies in both the heterogeneity of the mast cell and its heterogeneity of activation.[12] The mast cell is a 'key' inflammatory cell; it can be activated, releasing histamine and tryptase, by multiple mechanisms, including specific surface IgE activation (immune), complement activation and direct chemical (drug) effects.[13 14] With the demise of Cremophor-solubilized drugs (e.g. Althesin), the very severe life-threatening complement-(C3)-mediated effects have disappeared. The antigenicity of NMBAs is complex. Their pharmacological action involves the unique bisquaternary ammonium ions present in the most potent of these compounds. The interonium distance is also critical, indicating that these compounds act by bridging receptors at the neuromuscular junction. However, monoquaternary and even some monotertiary compounds have strong neuromuscular blocking properties and it may be that, in these cases, a pair of molecules acting together provide the necessary bridge. Immune triggering of mast cells and basophils requires an analogous bridging of adjacent, surface-bound specific IgE antibody molecules, but here antigenicity appears to be much more intimately attributed to the bisquaternary ions.[15] Thus, despite its well-established concentration-dependent release of plasma histamine, tubocurarine (monotertiary, monoquaternary) reactions are rarely immune-mediated, in sharp contrast to the behaviour of the bisquarternary drugs, succinylcholine and alcuronium. All the benzylisoquinolines exhibit the bisquaternary structure and are complex flexible molecules. High doses or fast administration lead to some plasma histamine release but the drugs are cardiovascularly stable. Atracurium readily produces a false positive weal-and-flare response unless care is taken with dilutions.

The aminosteroids vary in their ammonium ion distribution, do not release plasma histamine and rarely show a response to intradermal tests. Pancuronium, widely considered the safest NMBA in this respect, has less than critical interonium spacing (for blockade and possibly for immune bridging) while vecuronium and rocuronium are monotertiary, monoquaternary drugs. Thus, one would expect that fewer immune reactions will be observed with aminosteroids than with the benzylisoquinolines. Despite this, the overall clinical safety profiles of the two classes are virtually identical.[16] Just why some NMBAs are so antigenic is obscure; succinylcholine is generally considered the most antigenic,[3] despite its very close structural relationship to acetylcholine. Further, some patients appear to carry cross-reacting antibodies to succinylcholine without previous exposure to that agent, and these antibodies can persist for many years. It has been suggested that some patients become cross-sensitized to NMBAs as a result of the widespread exposure to the quaternary ammonium structure in nature (e.g. in foodstuffs and cosmetics) or perhaps as an autoimmune response to acetylcholine. However, most reactors have evidence of previous uneventful exposure to that drug and hence some sort of conventional immune sensitization.

The mechanisms of non-immunological mast cell activation are obscure. They may involve degranulation to varying degrees, with both histamine and tryptase release or the release of other mediators of the inflammatory response, the eicosanoids, without significant degranulation. While morphine is considered to be the classic opiate, its potential for releasing significant histamine appears unique and is not shared by the fentanyl compounds. The tertiary ammonium group of morphine provides a potent blocker *in vitro* of IgE antibodies to NMBAs. Local anaesthetic agents offer a halfway stage structurally to NMBAs, since they are bistertiary ammonium compounds. However, hypotension is most commonly the result of the local anaesthetic blockade of sympathetic fibres and not histamine release, although severe histaminoid responses have been encountered in Biers block procedures. The latter may relate to lipid membrane solubility or effects on sodium ion channels. Intradermal testing against these compounds has, at best, been equivocal.

The mechanism of non-immunological histamine and other mediator release appears to involve membrane-associated enzymes such as phospholipase A$_2$ and phospholipase C, involved in arachidonic acid synthesis and metabolism.[6] Antigenic responses to Diprivan may involve the effect of its detergent carrier on mast cell membranes as much as the active ingredient, diisopropylphenol. The initial solution of this drug in Cremophor by its then manufacturers, ICI, gave rise to a very high incidence of life-threatening complement-mediated histamine release and the drug had to be reformulated. Like the aminosteroid neuromuscular blocking drugs, Diprivan has a tendency to target the lungs as the principal shock organ. Indications of positive skin test results to Diprivan seem too high to account for genuine allergy to this simple phenol-based molecule, particularly when compared with the low incidence of classic sensitization to the barbiturate hypnotics.

Finally, one must address the problem of the site chosen for skin testing. Skin testing is usually carried out on the anterior face of the forearm or on the patient's back. The latter is favoured in France[17] since this skin is less exposed to environmental modifications and has similar characteristics in all individuals. Moneret-Vautrin and Laxenaire[17] also comment that the thin skin of the forearm is more likely to release histamine non-specifically. Drug test doses are selected on the basis of the concentration least likely to initiate a non-specific weal-and-flare response and these have largely been based on the observation of sequential concentration increases in reactors. The elegant studies reported by Levy and colleagues[9] must be tempered with the realization of the potential for volunteer sensitization, fortunately absent in this study. Mast cells isolated from different anatomical sites show marked heterogeneity when challenged with different neuromuscular blocking drugs *in vitro*. Thus, in studies reported by Marone and Stellato,[18] succinylcholine did not induce histamine release from any type of mast cell. Vecuronium induced minimal (5%) release from skin and lung mast cells but not at all from heart, in contrast to atracurium, which showed concentration-dependent release up to 46%. Commenting on the variation in the histamine-releasing activity of atracurium between individuals, now extended to other anaesthetic drugs, Stellato and colleagues introduced another variable: mast cell releasability factor.[19] Levy and his colleagues have extended these observations with skin biopsy and light and electron microscopy.[9] Here, the non-immune-induced weals revealed moderate degranulation when generated by *cis*-atracurium but not by rocuronium.

Skin test results should only be interpreted in terms of the tryptase-defined response and the patient's clinical history. Despite the comparative simplicity of the testing protocols,[8 17] considerable experience is necessary to exclude false positives and tests ideally should be carried out at centres with experience of drug testing, preferably by dermatologists or allergologists, and not as a 'one off' investigation by the anaesthetist. A current unsatisfactory trend is to test simultaneously a panel of all the usual neuromuscular blocking drugs with a view to elucidating future potential cross-reactivity. This panel is inevitably tested at the same dilution and not infrequently neat, at ampoule strength. Laboratory reports are often àccompanied by instruction for the patient not to receive any of the positive reactors, seriously compromising availability for future anaesthesia. Anecdotally, some anaesthetists whose patients have been screened for a whole battery of neuromuscular blocking drugs have received positive reports on a drug which has been used, without incident, to stabilize the shocked patient. This is either a non-immune response or genuine cross-reactivity but with antibody avidity insufficient to precipitate clinical anaphylaxis (cf. antibodies to house-dust mite and insect venom). Perhaps it is now time to re-examine such observations and their potential medicolegal significance. Prick testing may provide more specificity with the newer drugs while Fisher and Baldo have developed an intriguing radioimmunoassay using morphine bound in solid phase.[20] They claim this is a more sensitive and efficient test for the detection of IgE antibodies to NMBAs than individual drug-specific radioimmunoassay. Either way, the anaesthetist requires clear, nationally agreed, guidelines on the investigation of hypersensitivity-type reactions, the incidence of which, despite considerable advances in patient monitoring and new drugs over the last decade, has remained virtually unchanged.

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BJA

CLINICAL INVESTIGATIONS

Model-based automatic feedback control versus human control of end-tidal isoflurane concentration using low-flow anaesthesia

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We studied the clinical use of an automatic feedback control system to adjust the end-tidal anaesthetic concentration with a low-flow method. The end-tidal controller uses two input signals (the end-tidal and inspiratory concentrations) to control the isoflurane concentration in the fresh gas flow, using a model-based algorithm. We studied 22 ASA I–III patients during elective surgery lasting more than 2 h. The anaesthetist was asked to make four step changes of the target end-tidal concentration (+0.3, +0.6, –0.3, –0.6 vol%), either manually (Group A) or by setting the target value for the feedback controller (Group B), and then the control was changed and the step changes were repeated, in a crossover design. Eighty step changes with each control method were compared in terms of response time, maximal overshoot and stability. The automatic control system was more accurate and stable than the human controller for step increases and step decreases, with less overshoot/undershoot and greater stability [e.g. maximal overshoot 14.7 (SD 3.7)% and 18 (8.1)% respectively for +0.6 vol% step changes, and 19.8 (3.7)% and 30.7 (13.2)% respectively for +0.3 vol% step changes]. However, the automatic control system showed a faster response time than the manual method only with large increasing steps (e.g. 149 (32) s and 205 (57) s respectively for +0.6 vol% step changes) and was not different from manual control for decreasing steps. Automatic control of the end-tidal isoflurane concentration can be better than human control in a clinical setting, and this task could be done automatically.

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Computers are increasingly used for delivering anaesthesia and monitoring patients. Automatic control systems will probably soon help to improve safety and reduce repetitive tasks.[1–4]

Minimal and low-flow techniques of general anaesthesia are gaining popularity for different reasons. Cost and environmental issues[5 6] favour low-flow systems.[7] On the other hand, low-flow systems require more expertise, and because the changes in the fresh gas concentration have a delayed effect on the end-tidal concentration of inhalation agents, more adjustments of the vaporizer setting are needed. Automatic control of end-tidal anaesthetic concentration could facilitate low-flow anaesthesia and prove cost-effective.

The ideal variable for the control of anaesthesia is still a matter of debate. An indirect variable (e.g. mean arterial pressure, heart rate) is often chosen, and the EEG-derived bispectral index (BIS) has been used recently in a closed-loop feedback control system.[8] Another easily measurable variable is the end-tidal concentration of an inhalation anaesthetic. It closely represents the brain concentration and can easily be measured breath-to-breath by a non-invasive procedure. In clinical practice, a certain level of anaesthesia is sought by observing the end-tidal concentration of the volatile agent by adjusting the inspired anaesthetic concentration manually. Previous studies have shown that, by controlling the end-tidal concentration of the anaesthetic, induction is shortened and arterial and brain concentrations

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are more stable.[9] During the induction of anaesthesia, the inspired concentration is often set well above the desired brain tension to speed the induction process (the overpressure technique).[10]

We set a control system to adjust the end-tidal anaesthetic concentration for a variety of surgical interventions and patient characteristics, and compared it with manual control.

Methods

Patients

With institutional ethics committee approval and written, informed consent from the subjects, we studied 22 ASA I–III patients (18–75 yr) undergoing elective surgical procedures (neurosurgery, ENT, abdominal and orthopaedic surgery). We excluded patients with a history of coronary artery disease or with arterial hypertension that was poorly controlled.

The patients were given lorazepam 1–2 mg orally 30 min before induction of anaesthesia. An i.v. cannula was placed in a peripheral vein, and we monitored 3-lead ECG, arterial pressure (either non-invasively or invasively, at the discretion of the anaesthetist), and pulse oximetry. Anaesthesia was performed by experienced anaesthetists with more than 2 yr of training.

The patients were assigned randomly (by lot) to one of two treatment groups for the first phase of anaesthesia. Group A patients were anaesthetized by manual adjustment of the concentration of isoflurane. Group B patients were anaesthetized with an automatic feedback control system to adjust the end-tidal isoflurane concentration.

The anaesthetist was asked to make four step changes of the target end-tidal isoflurane concentration, either manually or by setting the target value for the feedback controller, after the beginning of surgery. The anaesthetists were in a realistic clinical situation and had to make the changes as best they could while fulfilling other clinical tasks. Before the first step change and after each subsequent step, an equilibration period of approximately 10 min was allowed so that a constant end-tidal concentration could be maintained. The end-tidal target concentration was increased in two steps (+0.3 and +0.6 vol%) and decreased in two steps (–0.3 and –0.6 vol%).

The sequence of the four step changes was chosen by the anaesthetist according to clinical needs and anticipated surgical stimulation, but the chosen step had to be sustained for a minimum time of 10 min. If the mean arterial blood pressure decreased by more than 20% after an increasing step-change, a single dose of ephedrine (5 mg i.v.) was allowed or an equivalent decreasing step-change of the end-tidal isoflurane concentration was sought. If the mean arterial pressure increased by more than 20% after a decreasing step change, additional fentanyl (1–2 μg kg^{-1}) was given.

After this first phase of four step changes, the method of adjusting the end-tidal isoflurane concentration was changed to the other method for a second phase, i.e. patients randomized to Group A (manual control) were now assigned to the automatic feedback control system for the next four step changes, and vice versa for Group B patients.

After a total of eight changes, the study finished and control continued with the second method. All the changes were made within the first 2 h of surgery. All changes were within a range of 0.3–1.2 vol% of the end-tidal isoflurane concentration.

Anaesthesia was induced with fentanyl (2 μg kg^{-1}) and thiopental (3–5 mg kg^{-1}). The trachea was intubated after muscle relaxation with vecuronium (0.1 mg kg^{-1}). Additional doses of vecuronium were given to maintain 0–2 responses of TOF stimulation at the ulnar nerve. After tracheal intubation, controlled ventilation was adjusted to maintain the end-tidal carbon dioxide at 4.5% (fixed respiratory rate of 10 per min, tidal volume variable), and anaesthesia was maintained with 70% N_2O in oxygen, isoflurane and boluses of fentanyl (1–2 μg kg^{-1}) as necessary.

After tracheal intubation, the fresh gas flow was set to 6 litre min^{-1}. Ten minutes later the flow was reduced to 1 litre min^{-1} and at the end of the surgery it was reset to 6 litre min^{-1} in both groups. The control system was started after the beginning of the operation. An equilibration period of 10 min was allowed for initialization of the controller before step changes of the end-tidal isoflurane concentration were undertaken. The sampling frequency for data collection was 10 per min, corresponding to a respiratory rate of 10 per min.

The control system

We used the Cicero workstation (Drägerwerke, Germany) with an isoflurane vaporizer (Dräger Vapour 19.3). It is able to monitor the following values: ECG, arterial pressure, pulse oximetry and sidestream measurements of oxygen, nitrous oxide, isoflurane and other inhalation agents. For safety reasons, isoflurane, nitrous oxide and oxygen concentrations were also measured with a sidestream anaesthetic gas analyser (Datex Capnomac; AVL, Switzerland). Both sampling lines were connected to a stopcock at the breathing filter (HME filter, nos 22 and 25; PALL, Switzerland) fitted to the endotracheal tube. All analysers were calibrated before use, according to the instructions of the manufacturers.

The end-tidal controller is a model-based state feedback controller (see Appendix A), uses two input signals (end-tidal and inspiratory isoflurane concentrations) and produces one output signal—the isoflurane concentration in the fresh gas supply, i.e. the vaporizer setting. The Dräger 19.3 vaporizer is adjusted by an external servo-motor. The servo-motor itself is driven by an analogue amplifier controlled by a PID (Proportional Integral Derivative for explanation see

Appendix A), which in turn is controlled by a conventional electronic interface. The vaporizer and the PID control system are calibrated so that known concentrations are delivered in response to the input voltage. Two Hi-Tech (Bronkhorst Hi-Tech, Ruurlo, Netherlands) nitrous oxide and oxygen mass flow controllers are used to supply a precise flow of gases. They are able to deliver gas flows between 0 and 10 litre min^{-1} with ±1% accuracy. The anaesthetist can control the feedback system with a touchscreen panel. This panel has buttons for the selection of the end-tidal isoflurane concentration and the fresh gas flow. The Cicero vaporizer and flowmeters are bypassed when the feedback control system is operating. However, the anaesthetist can revert to manual control at any time.

The control algorithms are implemented on a VME-board power PC using the real-time programming language XOberon (Institute of Robotics, Swiss Federal Institute of Technology, Zurich, Switzerland). Dedicated parts of the program are used to send data for display and storage to a standard PC via an Ethernet link.

Table 1 Patient characteristics and duration of surgery Values are mean (SD)

	Group A: manual control first	**Group B: automatic control first**
Sex		
Male	7	5
Female	4	6
Age (yr)	40.18 (19–68)	53 64 (31–75)
Weight (kg)	75.64 (17 33)	70.36 (14 35)
Duration of surgery (min)	233 64 (121.94)	204 09 (63.95)

Data analysis

The control of the end-tidal isoflurane concentration was judged by comparing the step changes of the target end-tidal isoflurane concentration under the two modes of control (manual/automatic feedback), using the following performance criteria (Tables 2 and 3).

1. Response time: time to reach the target value:

(a) increasing step change: time to reach the target value, from 10 to 90% of the step height (e.g. for an increasing step change of 0.6%, from 0.5 to 1.1%, the response time would be defined as the time to reach 1.04% from 0.56%);

(b) decreasing step change: time to reach the target value, from 10 to 90% of the step height (e.g. for a decreasing step change of 0.3%, from 0.8 to 0.5%, the response time would be defined as the time to reach 0.53 from 0.77%).

2. Maximal overshoot/undershoot: maximum amount the system overshoots or undershoots its target value, expressed as a percentage of the step height. Observation starts after the target value has been reached for the first time.

3. Stability: deviation of the measured end-tidal isoflurane concentration from the target value, expressed as percentage frequency distributions of the deviation (measured minus desired) of the end-tidal isoflurane concentration. Observation starts after the target value has been reached for the first time.

The number of changes of the vapour setting (≥0.05 vol%) was also recorded.

Numerical variables in the two groups were compared by the paired *t*-test when data were normally distributed, otherwise the Wilcoxon signed rank test was used. A P value <0.05 was considered statistically significant. The statistical package used was Sigma Stat, version 2.0 (Jandel Corporation, San Rafael, California, USA).

Table 2 Increasing step changes of F_E. Values are mean (SD) The sampling frequency for data collection was 10 per min, corresponding to a respiratory rate of 10 per min Response time=time to reach the target value, from 10 to 90% of the step height Maximum overshoot=maximum amount the system overshot its target value, expressed as a percentage of the step height. Stability=deviation of the measured end-tidal isoflurane concentration from the target value, expressed as percentage frequency distributions of the deviation (measured minus desired) of the end-tidal isoflurane concentration. *P<0 05

	Intended +0.3 vol% step change		**Intended +0.6 vol% step change**	
	Automatic control	**Manual control**	**Automatic control**	**Manual control**
Response time (s)	116 (20)*	71 (34)*	149 (32)*	205 (57)*
Maximal overshoot (%)	19 8 (3.7)*	30 7 (13.2)*	14.7 (3 7)	18 (8 1)
Number of changes of vapour setting	49 9 (7.4)*	14.7 (13.9)*	66.3 (11 9)*	14 4 (7 7)*

Table 3 Decreasing step changes of F_E Values are mean (SD) The sampling frequency for data collection was 10 per min, corresponding to a respiratory rate of 10 per min. *P<0 05

	Intended –0.3 vol% step change		**Intended –0.6 vol% step change**	
	Automatic control	**Manual control**	**Automatic control**	**Manual control**
Response time (s)	248 (169)	320 (260)	485 (230)	492 (190)
Maximal overshoot (%)	9.5 (3 3)*	14.2 (6.3)*	4 8 (1.7)*	7 2 (4 1)*
Number of changes of vapour setting	20 2 (14.3)*	8 7 (6.2)*	12 7 (7.7)	9.6 (4 1)

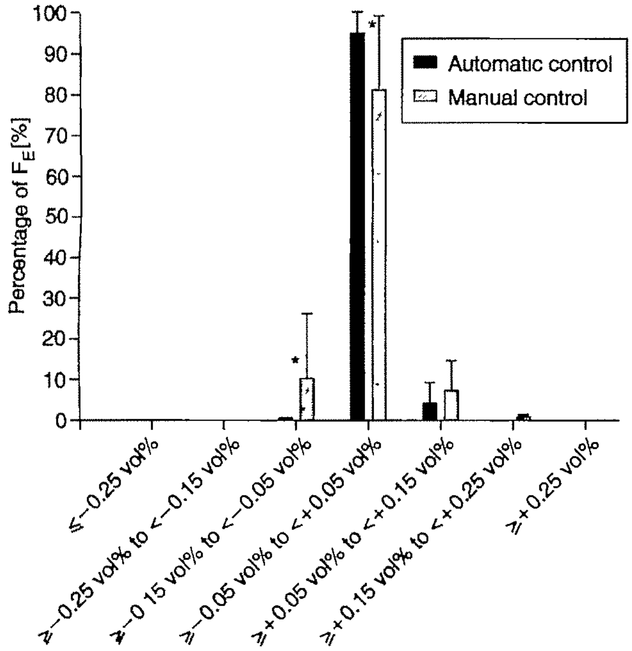

Fig 1 Target increases of +0.3 vol%. Stability of control obtained with manual control (shaded bars) and automatic control (black bars). The distribution histogram shows the proportion of samples that deviated from the intended value by increasing amounts. Mean and SD in each column. $^*P<0.05$

Results

The two groups were similar with respect to sex, age, weight and duration of surgery (Table 1).

In both groups, two patients had only one series of step changes because the operation finished early. The remaining 18 patients were studied after the protocol, i.e. they all had four step changes performed in the manual and in the automatic mode. Therefore, a total of 80 step changes were analysed in each group.

The performance of the feedback control was superior to that of the manual control in terms of overshoot and stability, with increasing as well as decreasing step changes (Tables 2 and 3 and Figs 1, 2, 3 and 4). The response time for the increasing step changes was shorter in the automatic mode for the larger steps only; for the smaller steps it was shorter in the manual mode. The response time for the decreasing step changes did not differ statistically between the two groups.

The automatic control of the end-tidal isoflurane concentration resulted in higher numbers of changes of the vapour setting, for increasing as well as decreasing step changes (only with decreasing steps of 0.6 vol% was the difference not statistically significant).

We observed a total of 19 artefacts during the automatic control mode. These artefacts were caused by the calibration process and were all handled successfully by the end-tidal controller. Figure 5 shows an untreated artefact during a pilot study. Figure 6 shows a suppressed artefact in a study patient.

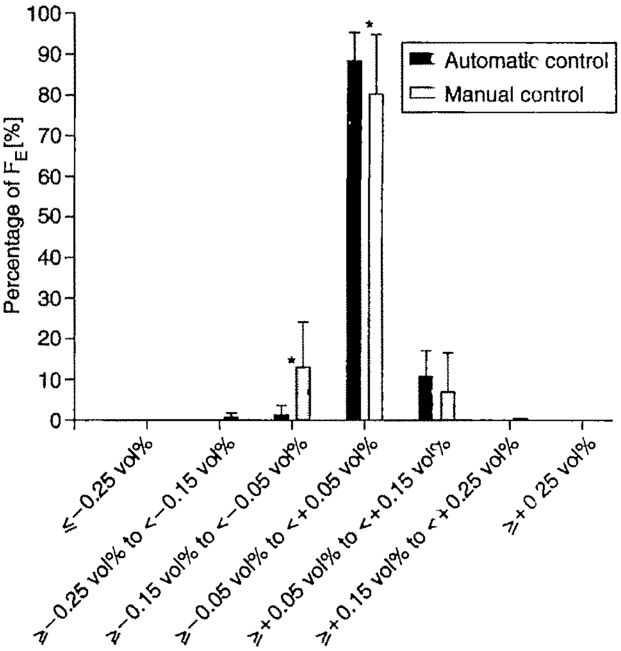

Fig 2 Target increases of +0.6 vol%. Stability of control obtained with manual control (shaded bars) and automatic control (black bars). The distribution histogram shows the proportion of samples that deviated from the intended value by increasing amounts. Mean and SD in each column. $^*P<0.05$

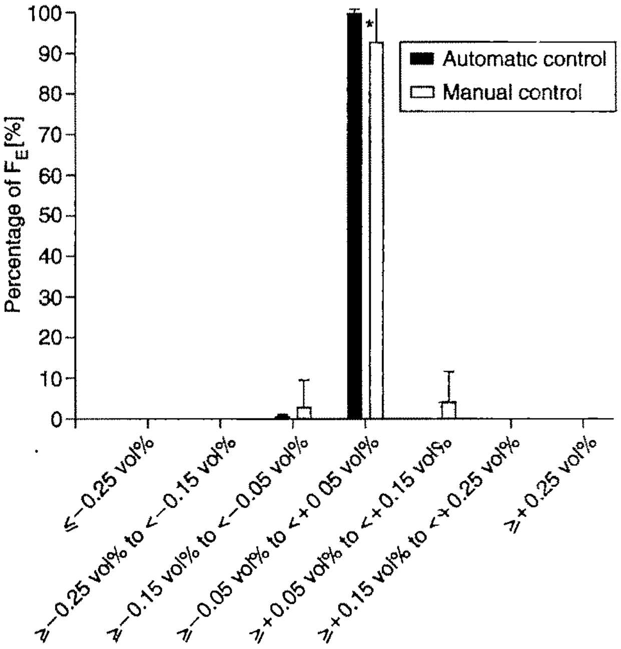

Fig 3 Target decreases of −0.3 vol%. Stability of control obtained with manual control (shaded bars) and automatic control (black bars). The distribution histogram shows the proportion of samples that deviated from the intended value by increasing amounts. Mean and SD in each column. $^*P<0.05$.

One patient in Group A and two patients in Group B required ephedrine to treat a decrease in mean arterial blood pressure of more than 20%.

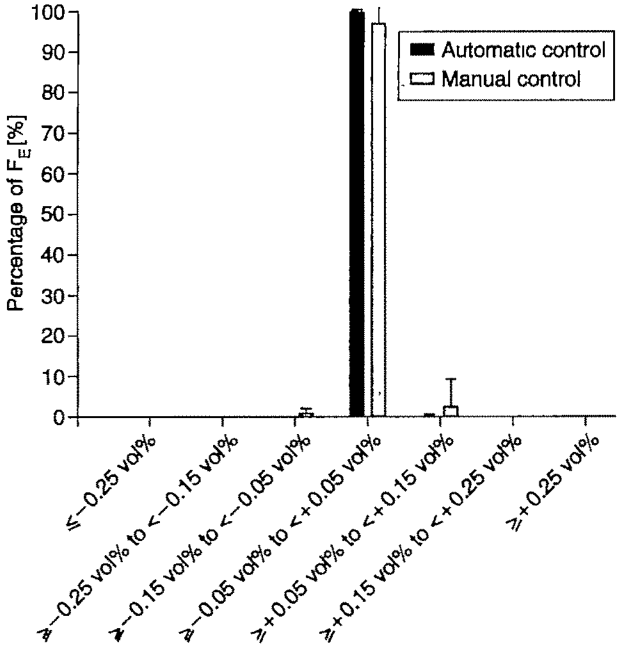

Fig 4 Target decreases of −0.6 vol%. Stability of control obtained with manual control (shaded bars) and automatic control (black bars). The distribution histogram shows the proportion of samples that deviated from the intended value by increasing amounts. Mean and SD in each column.

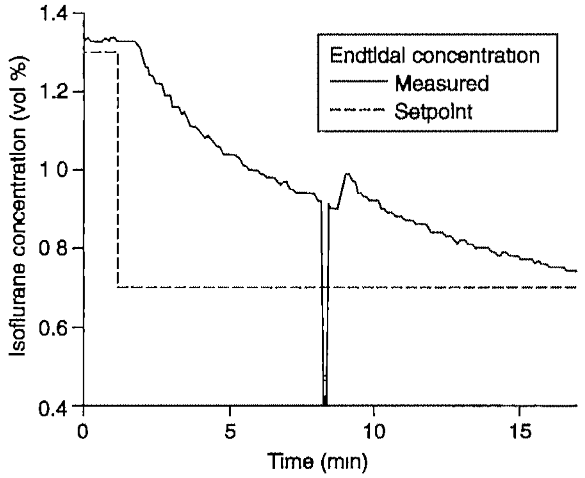

Fig 5 Example of an untreated calibration artefact, occurring during a decreasing step change in a pilot study. Because of the artefact, the end-tidal controller overshot the target value for a short period.

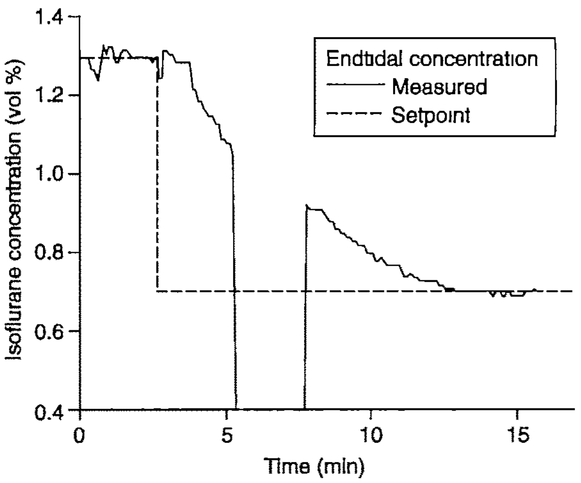

Fig 6 Example of the successful suppression of a calibration artefact, occurring during a decreasing step change in a study patient. Despite a prolonged calibration process, of approximately 2 min, the end-tidal isoflurane controller was not disturbed by the temporary lack of incoming data and the end-tidal isoflurane concentration slope continued to fall as if no data loss had occurred.

Discussion

The automatic control system of end-tidal isoflurane was generally faster, more stable and more accurate than human control.

The response time for increasing step changes was faster with automatic control than with manual control except for the small (+0.3 vol%) step changes. The slower response time of the automatic control for the small step changes was caused by the control algorithm, which only allowed a stepwise increase in the vaporizer setting, whereas with manual control the vaporizer setting was often immediately turned up to the maximum position. In a control system, there is a trade-off between the response time and the overshoot/stability of control. We judged that stability and accuracy of control should have priority over speed. Nevertheless, for the larger increasing step changes, the automatic control was faster and more reliable. With decreasing step changes there was no difference in the response time of the two modes. This is no surprise, as the rate of decrease of the end-tidal isoflurane concentration is determined by patient uptake and cannot be influenced directly unless the fresh gas flow is adjusted.

Stability and accuracy are the important clinical features of an automatic control system. Large changes in the control variable can either jeopardize the patient by an overdose or expose the patient to the risk of awareness. The clinical significance of the better performance of the automatic controller lies in the more reliable avoidance of minimal and maximal values of the control variable, whereas in the mid-range it does not make a great difference.

The model used in this study, with its 12 physiological compartments, is fairly complex. A less complex model derived from input/output measurements, like the one described by Yasuda and colleagues,[11] could perhaps give similar results. However, we plan to extend the automatic control application to children and less fit patients, for whom physiologically based models are easier to adjust to specific patient characteristics.

Complex control systems should reduce work and increase safety, but they will not do so in all situations or circumstances. An important safety issue is the handling of artefacts. Measurement artefacts can degrade controller performance or lead to hazardous situations for the patient.

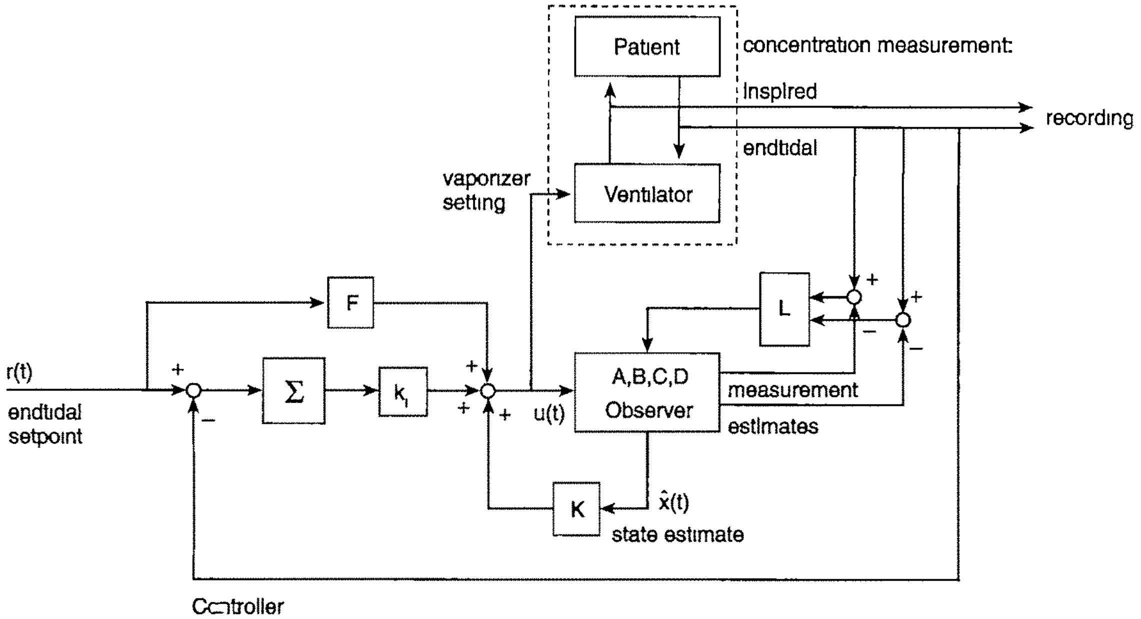

Fig 7 Structure of the model-based feedback controller. It consists of three components an observer (with the state feedback K and the correction gain L), the integrator Σ and the feedforward term F

Artefacts are quite common in clinical practice—for example, kinking of the gas sample tube. In our case, non-linear weighting of the error signal was used to make the model-based control algorithms tolerant of measurement artefacts.[12] When activated, the controller was able to suppress the influence of any artefact that occurred during the study.

Efforts to reduce the cost of inhalation agents by encouraging clinicians to use low fresh gas flows have not been very successful in the long term,[13] [14] mostly because of lack of continued feedback. Carefully constructed practice guidelines seem to be promising,[15] [16] but they can be difficult to introduce and are not in widespread use. A feedback control system for the end-tidal concentration of an inhalation agent would encourage low-flow systems and could be cost-effective.

Human control and intervention are still required to specify the appropriate depth of anaesthesia and to respond to crises. However, liberating the anaesthetist from those tasks that can be automated should improve safety by allowing the anaesthetist more time for other aspects of anaesthesia care.

Acknowledgements

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Appendix A

Model-based state feedback controller (Fig. 7)

Linear dynamic systems may be described by differential equations of the form

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}u(t)$$

$$\mathbf{y}(t) = \mathbf{C}\mathbf{x}(t) + \mathbf{D}u(t)$$

where $\mathbf{x}(t)$ is the state vector, $\dot{\mathbf{x}}(t)$ is the time derivative of $\mathbf{x}(t)$, $u(t)$ is the control input and $\mathbf{y}(t)$ is the measurement output. In our case, $\mathbf{x}(t)$ represents the partial pressure in the different body compartments and the breathing system and $u(t)$ represents the vaporizer position: $\mathbf{y}(t)$ is a vector composed of the measurements of inspired and expired isoflurane concentrations. The coefficients **A**, **B**, C and **D** are constant matrices. For details of the model, see Appendix B. Linear systems are idealizations since most real-world dynamic processes, and in particular physiological processes, are non-linear. However, most non-linear systems can be approximated by linear systems in a narrow working range. Even with larger working ranges it is often possible to achieve good controller performance with controller designs based on linearizations. The term 'state feedback' is used to describe a control algorithm in which the control signal is computed as a linear combination of various system states. Mathematically, the relationship between the controller output and the system states can be written as

$$u = -\mathbf{K}\mathbf{x}(t)$$

where **K** is again a constant matrix. This generic model-based state feedback controller is augmented with a feedforward term (F) and an integrator (Σ).[17] [18] The feedforward term accounts, for example, for the steady-state vaporizer position required to achieve a certain end-tidal target value. The integral term mainly compensates for modelling errors. Through these modifications, the state feedback control algorithm has some similarities to a classical PID controller. In such a controller, the control action has three components: (i) an action which is proportional (hence 'P') to the error between the set point and the system output; (ii) an action proportional to the integral (hence 'I') of this error; and (iii) an action that is proportional to the derivative (hence 'D') of this error. In the case of the augmented state feedback controller, the feedforward term (F) plays an analogous role as the P part. The integral term acts identically in both types of controller. The state feedback acts like a derivative term. The important difference is that it does not introduce just first-order derivative action but rather derivatives up to an order equal to the number of states in the state vector $\mathbf{x}(t)$. This makes it possible to design considerably more aggressive controllers.

Because in most cases the states of the system (e.g. the partial pressure of isoflurane within an organ) cannot be measured, an 'observer' (parallel model of the system to be controlled) is used to compute an estimate of the states ($\hat{\mathbf{x}}(t)$). This state estimate is then used in the control algorithm instead of the actual state. The state estimates usually differ from the true states because an observer cannot fully describe the reality and the initial conditions are not known precisely. To achieve fast convergence of the state estimates towards the true states, a correction gain (L) is introduced. This gain leads to correction of the state estimates based on the difference between the measurements and the predictions of the parallel model. Note that in our case the measurements refer to the measurement vector $\mathbf{y}(t)$, which contains the inspired as well as the end-tidal isoflurane concentration measurement. Typically, L is a constant gain which must be chosen so that the rate of convergence of the state estimation is faster than the desired response of the controller. Using a non-linear-modified gain, however, artefacts can be rejected easily.[12]

Appendix B

Model

The pharmacokinetic and pharmacodynamic model description was obtained by adjusting the compartmental model for halothane described by Smith and colleagues[19] to isoflurane and by augmenting it with a dynamic representation of the respiratory circuit. The adjustment to isoflurane was done by means of published isoflurane partition coefficients.[20] The physiological model part describes the time-course of the partial pressure of isoflurane in 12 body compartments. Nine compartments represent different organs grouped according to their pharmacokinetic properties with respect to isoflurane. One compartment represents the gas exchange in the lung, and an arterial and a venous compartment are introduced to interconnect the lung and the body compartments. Together with the equation for the anaesthetic partial pressure in the respirator circuit, the state vector $\mathbf{x}(t)$ is derived as follows:

$$\mathbf{x}(t) = [p_1(t) \ldots p_9(t)\ p_{Lung}(t)\ p_{Art}(t)\ p_{Ven}(t)\ p_{Resp}(t)].$$

The dynamics of the pressure in a body compartment is described by

$$\dot{p}_i(t) = \frac{\lambda_b q_i(t)}{\tilde{V}_i}[p_{Art}(t) - p_i(t)]$$

where λ_b is the solubility of isoflurane in blood, $q_i(t)$ is the blood flow through the compartment, and $\tilde{V}_i$ is a virtual distribution volume obtained as the sum of the blood and tissue volumes of the compartment, weighted with their respective solubilities. The partial pressure dynamics in the lung is given by

$$\dot{p}_{Lung}(t) = \frac{1}{\tilde{V}_{Lung}}[\lambda_b CO(t)\{p_{Ven}(t) - p_{Lung}(t)\} +$$
$$q_{AV}\{p_{Resp}(t) - p_{Lung}(t)\}]$$

where $CO(t)$ is cardiac output and q_{AV} is the alveolar ventilation, which is given by

$$q_{AV} = f_R(V_A - V_{AD})$$

where f_R is the respiratory frequency.

The equation for the arterial partial pressure is

$$\dot{p}_{Art}(t) = \frac{\lambda_b CO(t)}{\tilde{V}_{Art}}[l_s p_{Ven}(t) + (1 - l_s)p_{Lung}(t) - p_{Art}(t)]$$

where l_s is the shunt in the lung. The venous partial pressure is

$$\dot{p}_{Ven}(t) = \frac{\lambda_b}{\tilde{V}_{Vent}}[\sum q_i(t)p_i(t) - CO(t)p_{Ven}(t)].$$

The above equations suggest that $CO(t)$ and $q_i(t)$ are measurable as time evolves. This is not the case. Pharmacodynamic relations are used instead to compute these quantities. The corresponding equations are

$$CO(t) = CO_0(1 + \alpha_1 p_1 + \alpha_2 p_2 + \alpha_3 p_{Art})$$

for the cardiac output and

$$g_i(t) = g_{i,0}(1 + \beta_i p_i)$$

for the conductivities of the different body compartments, from which $q_i(t)$ may be computed.

Finally, the dynamic equation of the respirator circuit is given by

$$\dot{p}_{Resp}(t) = \frac{FF}{V_R}p_{Vap}(t) + q_{AV}[p_{Lung}(t) - p_{Resp}(t)] -$$
$$\frac{FF - \Delta(t)}{V_R}p_{endt}(t)$$

where FF is the fresh gas flow, V_R is the circuit volume, $p_{Vap}(t)$ is the vaporizer setting, and $\Delta(t)$ is the net uptake of gas. The quantities FF and $p_{Vap}(t)$ are known because they are set, and $\Delta(t)$ is available from the literature.[21] $p_{endt}(t)$ is the end-tidal concentration and is given by

$$p_{endt}(t) = \frac{V_{AD}}{V_A} p_{Resp}(t) + \left(1 - \frac{V_{AD}}{V_A}\right) p_{Lung}(t)$$

where V_A is the total alveolar space and V_{AD} is the alveolar deadspace. For the design of the controller, linearizations of these equations yield the system matrices **A**, **B**, **C** and **D**. To give a more detailed description of the model in terms of parameters and validations is beyond the scope of this appendix. The interested reader is referred to reference 22 for such details.

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Ropivacaine 0.2% *versus* bupivacaine 0.1% with fentanyl: a double blind comparison for analgesia during labour

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We have performed a randomized, double-blind comparison of two epidural drug regimens for analgesia in labour. In the bupivacaine group (BUPIV), 101 healthy parturients received 0.1% bupivacaine with fentanyl 2 μg ml^{-1}. In the ropivacaine group (ROPIV), 102 women received 0.2% ropivacaine. Both groups received an initial loading dose of 15 ml, a continuous infusion of 8 ml h^{-1}, and top-ups of 10 ml. Breakthrough pain not responding to a routine top-up was treated with an 'escape' top-up of 10 ml 0.25% bupivacaine. The two groups were compared for complete analgesia at 30 min, routine and 'escape' top-up requirements, midwife assessment of analgesic efficacy, delivery mode, patient visual analogue scores (VAS) for first and second stage analgesia, overall satisfaction, and patient assessment of motor blockade. Patients receiving ropivacaine received fewer routine top-ups (median 1.0 *vs.* 2.0, P=0.001) and fewer escape top-ups (9.8% *vs.* 21.8%, P=0.02). The ropivacaine group was more likely to be pain free in the first stage (51% *vs.* 33.7%, P=0.01). There were no significant differences in patients' assessment of motor block or mode of delivery between the groups. Pain relief and satisfaction scores from midwives and patients were consistently better in the ropivacaine group, but did not reach statistical significance.

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The most popular method of maintaining epidural analgesia for labour in the UK is a continuous infusion of low-dose bupivacaine with an opioid.[1] The addition of the opioid allows the dose of bupivacaine to be reduced without adversely affecting the quality of analgesia.[2] Reducing the dose of bupivacaine significantly reduces the incidence and severity of maternal motor neural blockade.[3] Increased mobility during epidural analgesia has been associated with greater maternal satisfaction.[3 4] However, the use of opioids in epidural infusions is not without adverse effects. Pruritus is the most common of these,[3] and maternal hypoxaemia during the second stage of labour has been reported.[5]

Ropivacaine has been introduced into clinical practice with the claim that it causes less motor block than bupivacaine.[6 7] If true, this raises the possibility of producing the same high quality analgesia, modest motor blockade and high maternal satisfaction with plain ropivacaine as with a low-dose bupivacaine/opioid mixture, thereby avoiding the opioid side effects. The most common bupivacaine/opioid mixture used in the UK is 0.1% bupivacaine with fentanyl 2 μg ml^{-1}.[1] From minimum local analgesic concentration (MLAC) studies, it can be inferred that 0.2% ropivacaine is the analgesic equivalent of 0.1% bupivacaine with fentanyl 2 μg ml^{-1}.[8–10] This concentration of ropivacaine has been used effectively in labour epidural analgesia.[11] Therefore, we decided to compare 0.2% ropivacaine with 0.1% bupivacaine plus fentanyl 2 μg ml^{-1} for quality of analgesia, mode of delivery, patient assessment of motor blockade, midwife and maternal satisfaction in a randomised double blind trial.

Methods

A power calculation for this study is difficult because of the many outcomes under consideration. However, an audit of 570 epidurals prior to this study showed that 76% of women receiving a bupivacaine/fentanyl epidural recorded 'excellent satisfaction' (the best of a four point descriptive scale). To find a difference of 20% in the percentage of women recording this score between the study groups we therefore needed to study 200 women to achieve a power of 0.8. Using data from other studies we calculated that this sample size was also sufficient to detect a difference 20% for women recording minimal motor block.[3 12] The study was approved

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by the local Clinical Research (Ethics) Committee. Patient information sheets were then distributed in antenatal clinics, parentcraft classes, and all delivery rooms.

All women requesting epidural analgesia were considered eligible for the study, excluding those refusing consent or having allergies to any of the study drugs. After providing informed, written consent, randomization was performed by sealed envelope into one of two treatment groups. Using blinded syringes, patients in the BUPIV group received 0.1% bupivacaine with fentanyl 2 µg ml^{-1}, and the ROPIV group received 0.2% ropivacaine. All patients received an initial loading dose of 15 ml, with the first 5 ml acting as a test dose for intrathecal catheter placement. This was followed by an infusion of 8 ml h^{-1} with top-ups of 10 ml as required. 'Escape' top ups of 10 ml 0.25% bupivacaine were prescribed for pain that did not respond to top-ups of the study drugs.

Patient characteristics, procedural, and outcome data were collected using the Wansbeck Epidural Audit System as previously described.[12] This computer program generates epidural charts, midwife assessment forms, and patient follow-up questionnaires, whilst simultaneously feeding a database. Mode of delivery, midwife assessment of analgesia, 'yes/no' for complete analgesia at 30 min after the loading dose, and top-up requirements were recorded contemporaneously. Patient visual analogue scores for first and second stage pain, their assessment of motor block, and overall satisfaction with the epidural were obtained 24 h after delivery by an anaesthetist blinded to the treatment regimen.

Data were collated using Microsoft Access Version 2.0 and Excel Version 5.0. Parametric data were compared using two sided, two sample *t*-tests and non-parametric data were compared using the Mann-Whitney *U* test. Discrete data were compared by Chi-Square, with odds ratios and confidence intervals calculated where appropriate. Significance level was taken at $P<0.05$. Statistical analysis was performed on SPSS Version 6.0 for Windows.

Table 1 Patient characteristics and duration of labour after epidural siting as mean (SD or range) or number *P value by two-sided unpaired Student *t* test †P value by chi-square test with 1 df

	BUPIV group (*n*=101)	ROPIV group (*n*=102)	*P*
Age (yr)	28 (6–44)	29 (16–43)	0 54*
Height (cm)	159 7 (6 8)	161 0 (4.9)	0 11*
Weight (kg)	77 5 (15 1)	77 0 (11 1)	0 79*
Primiparous (*n*)	75	71	0 45†
Multiparous (*n*)	26	31	0 45†
Duration of labour (min)	413 4 (186 2)	400 1 (217 0)	0 64†

Table 2 Mode of delivery in the BUPIV and ROPIV groups (number) SVD=spontaneous vaginal delivery OR=odds ratio, *Chi-square test with 1 df

	BUPIV group (*n*=101)	ROPIV group (*n*=102)	OR (95% CI)	Chi statistic*	*P*
SVD	56	50	1 29 (0 75–2 25)	0 84	0 37
Instrumental	24	30	0 75 (0 40–1 40)	0 83	0 36
Caesarean section	21	22	0 95 (0 49–1 87)	0 02	0 89

Results

Complete data were obtained for 203 of the 212 patients who were recruited to the study. No patients experienced inadvertent dural puncture, required an epidural resite, or were withdrawn from the study. There were no significant differences between the groups for patient characteristics (Table 1) or mode of delivery (Table 2). Patients in the BUPIV group required significantly more epidural top-ups (median 2.0 *vs.* 1.0, P=0.001) and were twice as likely to require an escape top-up (21.8% *vs.* 9.8%, P=0.02) compared with the ROPIV group (Table 3). Whilst there were no differences between the two groups for the proportion of women who were pain-free at 30 min, significantly more women remained pain-free throughout the first stage of labour in the ROPIV group compared with the BUPIV group (51% *vs.* 33.7%, p=0.01, Table 4). There were no differences between the two groups for pain scores in the second stage of labour.

There were no differences between the two groups for midwife and patient overall satisfaction with pain relief (Tables 5 and 6). Whilst a higher percentage of women in the BUPIV group had minimal motor block compared with the ROPIV group, this difference was not statistically significant (Table 7).

Discussion

There are several aspects of our study design that warrant discussion. Many of the outcomes are of a subjective nature and were recorded retrospectively. However, the fact that several large UK units use the same clinical audit software indicates that many practitioners consider these outcomes of interest. In practice, patients seem very comfortable with the follow up questionnaire and have no difficulty in making their choice from the descriptive scales.

Table 3 Epidural top-ups required in the BUPIV and ROPIV groups (number or median (range)) OR=odds ratio, *Chi-square test with 1 df, †Mann-Whitney *U* test

	BUPIV group (*n*=101)	ROPIV group (*n*= 102)	OR (95% CI)	Chi statistic*	*P*
No of patients who required escape top-up	22	10	2 56 (1 14–5 73)	5 48	0 02*
No of top-ups given per patient	2 (0–14)	1 (0–7)	–	–	0 001†

Table 4 Quality of analgesia during labour in the BUPIV and ROPIV groups (number). OR=odds ratio; *Chi-square test with 1 df

	BUPIV group (n=101)	**ROPIV group (n=102)**	**OR (95% CI)**	**Chi statistic***	***P***
Pain free at 30 min	84	81	1.28 (0.63–2.60)	0.47	0.50
Analgesia during 1st stage of labour:					
VAS=0 mm	34	52	0.49 (0.28–0.86)	6.23	0.01
VAS <10 mm	52	61	0.71 (0.41–1.24)	1.42	0.24
VAS <30 mm	77	84	0.72 (0.36–1.43)	1.16	0.27
Missing data	3	2			
Analgesia during 2nd stage of labour					
VAS=0 mm	33	40	0.75 (0.42–1.34)	0.94	0.32
VAS <10 mm	41	46	0.83 (0.48–1.45)	0.42	0.53
VAS <30 mm	61	69	0.73 (0.41–1.30)	1.16	0.27
Missing data or sectioned prior to 2nd stage	11	12			

Table 5 Midwife assessment of pain relief in the BUPIV and ROPIV groups (number). Chi-square trend=0.81 (1 df), P=0.32. OR=odds ratio, *Chi-square test with 1 df

	BUPIV group (n=101)	**ROPIV group (n=102)**	**OR (95% CI)**	**Chi statistic***	***P***
Excellent	47	54	0.77 (0.45–1.34)	0.83	0.37
Satisfactory	32	27	1.29 (0.70–2.37)	0.67	0.40
Somewhat unsatisfactory	10	8	1.29 (0.49–3.42)	0.26	0.63
Unsatisfactory	6	3	2.1 (0.51–8.57)	1.07	0.32
Missing data	6	10			

Table 6 Patient overall assessment of pain relief in the BUPIV and ROPIV groups (number). Chi-square trend=0.18 (1 df), P=0.65. OR=odds ratio; *Chi-square test with 1 df

	BUPIV group (n=101)	**ROPIV group (n=102)**	**OR (95% CI)**	**Chi statistic**	***P***
Excellent	68	75	0.74 (0.40–1.36)	0.94	0.33
Satisfactory	23	21	1.14 (0.58–2.22)	0.14	0.70
Somewhat unsatisfactory	5	1	5.26 (0.60–45.9)	2.78	0.10
Unsatisfactory	2	4	0.49 (0.10–2.76)	0.67	0.41
Missing data	3	1			

Table 7 Patient assessment of motor block in the BUPIV and ROPIV groups (number). Chi-square trend=0.88 (1 df), P=0.34. OR=odds ratio; *Chi-square test with 1 df

Motor block	**BUPIV group (n=101)**	**ROPIV group (n=102)**	**OR (95% CI)**	**Chi statistic***	***P***
Minimal	52	43	1.46 (0.84–2.50)	1.77	0.18
Able to walk	8	2			
Mobile in bed	44	41			
Moderate	41	52	0.66 (0.38–1.15)	2.21	0.14
Needed some help to move	29	40			
Dependent on help to move	12	12			
Severe	5	5	1.01 (0.28–3.60)	<0.01	0.99
Could just move legs	2	2			
No leg movement at all	3	3			
Missing data	3	2			

Contemporaneous, hourly visual analogue scores for pain with formal modified Bromage scale motor block assessments might be the academic ideal, but are not feasible in the context of a relatively large study in a busy unit. We argue that subjective assessments of analgesia and motor block, however flawed scientifically, are how patients judge their experience and therefore should be of primary concern.

The focus of this study was to compare the two techniques from the perspective of midwives and patients in the context of a standard technique used in a busy unit. It was never our aim to formally assess pharmacokinetic and dynamic variables such as speed of onset, block heights, and objective motor block. Similarly, we justify the recruitment of all women into this study, regardless of parity and stage of labour, because it is our clinical practice to use a single starting regimen for all women requesting epidural analgesia.

No formal comparisons were made of side effects such as pruritis, nausea, vomiting, and hypotension between the groups. This decision was made because it can be safely assumed that the bupivacaine/fentanyl combination will cause pruritis in a percentage of women, and plain ropivacaine will not. An audit of the incidence of clinically significant hypotension using these treatments revealed such a low incidence that a much larger study would be required to separate the treatments on haemodynamic grounds. Similarly, given that the incidence of nausea and vomiting at some time during childbirth approaches 100%, it would be difficult to assess the causative contribution of the epidurals.

One outcome not considered was the performance of epidurals when converted to anaesthesia for Caesarean section. This is because we have a very low threshold for using spinal anaesthesia despite the presence of an existing epidural in our unit. This policy follows a three year audit showing that *all* cases of inadequate regional anaesthesia involved topped-up epidurals. Conversion to spinal anaesthesia is not therefore a meaningful measure of epidural performance in our unit.

The principal findings of this study are that 0.2% ropivacaine produces better first stage analgesia than 0.1% bupivacaine with fentanyl 2 μg ml^{-1} and requires fewer routine and escape top-ups. This may be due to the longer duration of action of ropivacaine.[13] Whatever the explanation, this challenges our earlier assumption that an opioid is necessary to minimise missed segments, perineal pressure, and to maximise efficacy and satisfaction. The increased motor block in the ropivacaine group was not statistically significant, but the study was probably underpowered for this point. For the size of difference in minimal motor block found in this study, a two sided test to detect a significant difference at $P<0.05$ with a power of 0.8 would have required the recruitment of at least 800 women. However, even if the ropivacaine regimen did cause more motor block, this did not adversely affect patient satisfaction. Thus another widely held assumption, that satisfaction is strongly related to mobility, is challenged.

This study cannot be used in isolation to make comparative judgements about plain ropivacaine and bupivacaine in labour epidurals. To answer questions about relative motor block effects and overall efficacy requires a comparison of MLAC equivalent plain solutions, such as 0.2% ropivacaine and 0.12% bupivacaine. So, despite the encouraging results in this study, a final judgement on the value of ropivacaine in obstetric practice is not yet possible.

In summary, the results from our study support other work[11] suggesting that 0.2% ropivacaine is a suitable choice for labour epidurals. The assumption that an added opioid is always necessary to achieve good analgesia, high maternal satisfaction, and acceptable motor block is challenged and warrants further investigation.

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Ropivacaine plasma concentrations during 120-hour epidural infusion

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The pharmacokinetics of ropivacaine were evaluated during long-term continuous epidural analgesia (CEDA) for about 120 h. The total and free plasma concentrations of ropivacaine and the α_1-acid glycoprotein (AAG) concentration were measured in 12 patients after total knee arthroplasty. The infusion rate was adjusted according to patients' analgesic needs or side effects. The mean (SD) rate of infusion of ropivacaine (Naropin 2 mg ml^{-1}) was 14.6 (3.2) mg h^{-1} on the day of surgery and was increased after surgery to 15.4 (4.4) mg h^{-1} on days 1–5. This was equivalent to an absolute dose of 1786 (553) mg of ropivacaine over the entire infusion period. After an initial increase, the mean free ropivacaine plasma concentration nearly plateaued and than decreased slightly after approximately 70 h. The individual peak free plasma concentration was 0.096 (0.034) µg ml^{-1}. The highest individual free plasma concentration was 0.16 µg ml^{-1}. The individual peak total plasma concentration, 4.1 (1.2) µg ml^{-1}, was achieved after 67.7 (16.5) h, although the AAG concentration increased throughout the observation period. Our data support the safety and efficacy of long-term ropivacaine CEDA.

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Ropivacaine (Naropin) is a long-acting amide local anaesthetic, structurally closely related to bupivacaine. It appears to produce less blockade of motor fibres than bupivacaine but with similar sensory blockade.[1 2] Earlier studies[3 4] suggest an increased safety margin before onset of toxic side effects after treatment with ropivacaine, compared with other local anaesthetics. Other studies have shown that ropivacaine is suitable for postoperative epidural analgesia.[5–7]

The pharmacokinetics of ropivacaine after intravenous infusion,[4 8] after infiltration[9] and during epidural application[10 11] have been demonstrated. Collectively, previous studies concerning continuous epidural analgesia (CEDA),[12–15] suggest a gradual increase in the plasma concentration of ropivacaine. However, these observations concerned periods of ≤72 h. The pharmacokinetics of long-term ropivacaine application remain unclear, therefore. As many operations require longer-lasting CEDA,[16 17] the principal aim of this study was to evaluate the pharmacokinetics of ropivacaine 2 mg ml^{-1} for CEDA lasting about 120 h, with dose adjustments being made according to clinical need.

Methods

Patients

After obtaining approval from the Ethics Committee of the Otto von Guericke University, Magdeburg, and written informed consent, we studied 15 patients after total knee arthroplasty. Patients were considered eligible for the study if they were aged 18–85 yr, weighed 50–120 kg and were of ASA status I–III. None of the patients had intrinsic abnormalities of hepatic or renal function, or had neurological or mental diseases or any conditions that would interfere with the ability to assess pain after surgery. Only patients who received one particular type of joint replacement (Natural Knee endoprosthesis; Sulzer Medica, Switzerland) were included.

Drug treatment and clinical assessment

Premedication consisted of midazolam and atropine sulfate, injected intramuscularly within 30 min before the patient's arrival in the anaesthetic room. Before surgery, an epidural catheter was placed at level L3–4 or L4–5 in each patient.

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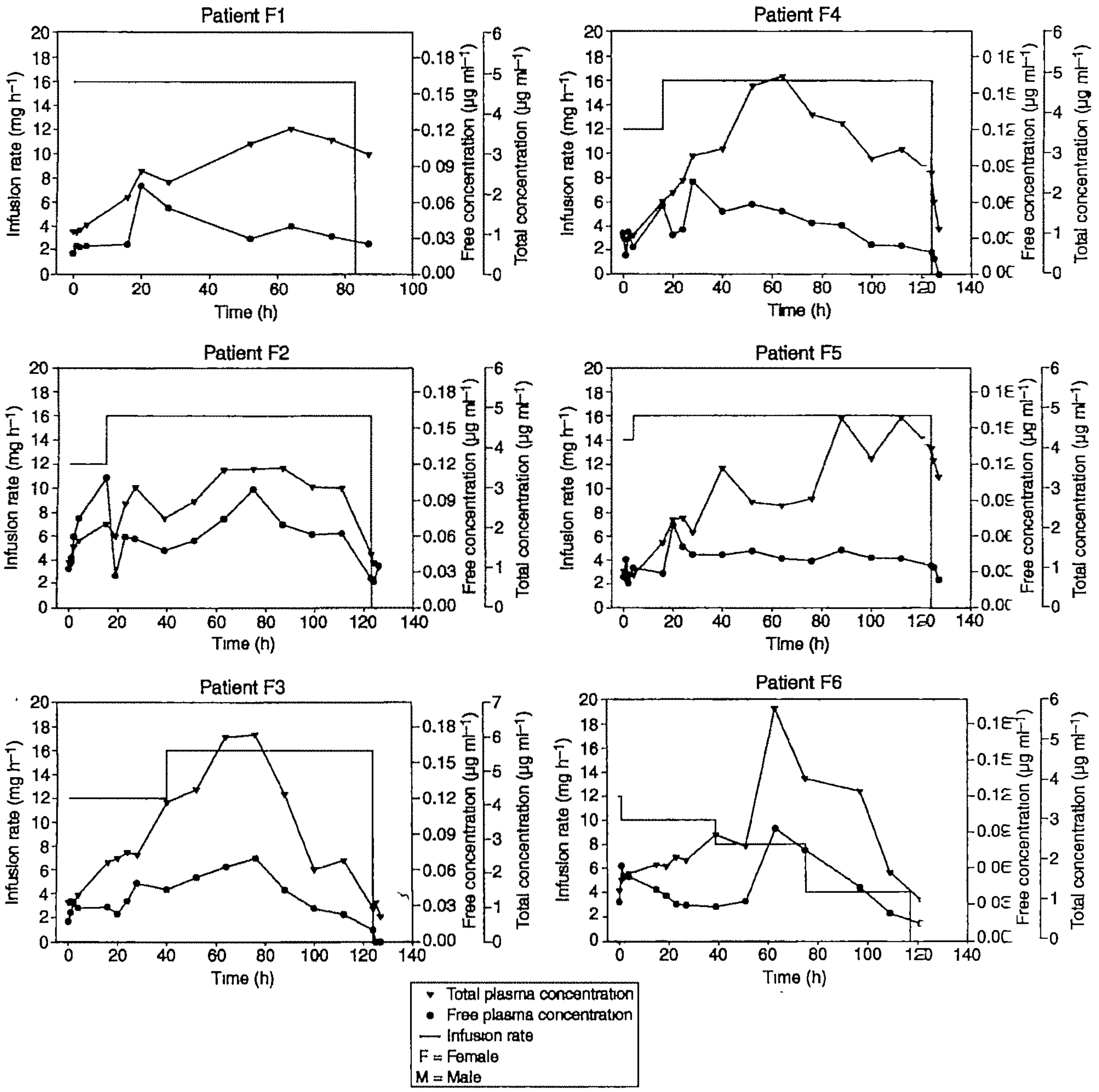

Fig 1 Individual time course of the total and free plasma concentration and the epidural infusion rate of ropivacaine using Naropin 2 mg ml^{-1}.

The catheter was inserted through an 18-gauge Touhy needle in a cephalic direction 3–4 cm from the epidural space. After insertion, the catheter was fixed by tunnelling it subcutaneously for 5 cm and suturing it in place. If there was no evidence of intrathecal position after giving a test dose of 30 mg ropivacaine (10 mg ml^{-1}), all patients were given a full loading dose of ropivacaine 120–150 mg. As a guideline for dosage, 1–1.2 ml ropivacaine (10 mg ml^{-1}) was used per segment. Before surgery, loss of temperature sensation was used to confirm an adequate upper level of sensory blockade. During surgery, midazolam was used to sedate patients. Additional epidural ropivacaine was given if required.

After operation, continuous epidural infusion of ropivacaine (Naropin 2 mg ml^{-1}) was started when the motor blockade decreased to 0–1 on the modified Bromage scale[16] or when the sensory blockade dropped below the T8–T10 level. We started with an initial infusion rate of ropivacaine 12 mg h^{-1} (2 mg ml^{-1}). The infusion rate was adjusted to ensure an adequate clinical level of sensory blockade without motor blockade. The initial infusion rate was increased if the sensory level declined below the level of T12 or if the visual analogue scale (VAS) pain scores increased to >5. Before increasing the infusion rate, a bolus of ropivacaine 4 mg (2 mg ml^{-1}) was given.

Table 1 Details of the postoperative epidural infusion of ropivacaine (Naropin 2 mg ml^{-1}) [a]Times at which infusion rate was changed are given in hours after the beginning of infusion F = female, M = male

Patient	F1	F2	F3	F4	F5	F6	F7	F8	F9	M1	M2	M3
Infusion duration (h)	84	123	124	124	124	108	126	134	84	136	124	126
Total dose (mg)	1344	1908	1824	1920	1992	692	1816	1464	1700	2714	2812	1348
Changes in infusion rate[a]												
Increases		15	40	16	4		18	16	20, 40	4	20	18
Decreases						39, 72	98	64, 76	16, 28			4, 42

All patients were connected to a patient-controlled analgesia device (PCA System, Vygon, Aachen, Germany) delivering piritramide. The PCA system was set to deliver piritramide 1 mg per bolus with a lock-out time of 5 min.

Blood sampling and drug assay

Peripheral venous blood samples were taken before the start of epidural injection (time 0) and 1, 2 and 4 h after time 0 on the day of the operation. On the day after surgery, samples were taken at 8 a.m., 12 noon, 4 p.m. and 8 p.m. Samples were also taken on days 2–5 after surgery at 8 a.m. and 8 p.m., at the end of the infusion and finally 1 and 3 h after infusion was stopped.

All plasma samples were frozen within 1 h of collection and stored at –20°C until assayed. Plasma concentrations were determined at the Justus von Liebig University, Giessen, Germany. The total and free plasma concentrations of ropivacaine base were determined using high pressure liquid chromatography and ultraviolet detection (HPLC/UV), according to the method described by Adams and colleagues,[18] with a lower limit of determination of <0.01 µg ml^{-1} and a coefficient of variance of 4%. Recovery rates of 92–93% were achieved. Free plasma concentrations were determined after ultrafiltration of the samples using the Amicon micropartition system (MPS-1; Amicon, Beverly, MA, USA). After separation, 600–800 µl of plasma protein free ultrafiltrate was extracted. Any pH shift was avoided before ultrafiltration. The α_1-acid glycoprotein (AAG) concentrations were measured using a rate nephelometric immunoassay technique (Nephelometer BN 100; Behring, Schwalbach, Germany). The lower limit of quantification was set at 0.01 µg ml^{-1} with an interassay precision of 2.0%.

The patients' data were recorded and calculated using Microsoft Excel 7.0. All results are expressed as mean (SD) unless otherwise stated. The graphs were created using Sigmaplot 4.0 (Jandel Scientific, San Rafael, CA, USA).

Results

Epidural anaesthesia was satisfactory in all patients. After the start of surgery, one patient required an additional dose of 30 mg ropivacaine (10 mg ml^{-1}). For three patients, CEDA was stopped prematurely for the following technical reasons: epidural catheter displacement; interruption of infusion for 3 h; and misfilling of the injection pump. Therefore, plasma concentrations of ropivacaine and the AAG concentration were measured in 12 patients. The mean (SD) patient age was 68.8 (7.28) yr, height 164 (7) cm and weight 85 (16) kg. The dose of ropivacaine (10 mg ml^{-1}) used for epidural anaesthesia was 156 (18) mg. A sensory level of T6±1 was achieved. The duration of surgery was 72.9 (19.6) min.

Pharmacokinetic evaluation

Postoperative epidural ropivacaine infusion was started 5.0 (1.17) h after the first bolus dose of ropivacaine for surgery. The ropivacaine (2 mg ml^{-1}) infusion rate was 14.6 (3.2) mg h^{-1} on the day of surgery and was increased to 15.4 ± 4.4 mg h^{-1} on days 1–5 after surgery. This was equivalent to a ropivacaine dose of 1786 (553) mg. The time course of the infusion rate and the plasma concentrations of ropivacaine is shown in Fig. 1. In two patients (F1 and F9), epidural infusion was stopped after 84 h, at the request of the patients. In five patients (F2, F4, F5, M1 and M2), no dose adjustment was necessary for ≥100 h. The infusion rate was reduced in three patients (F6, F9 and M3), increased in three patients (F2, F3 and M2), and changed in both directions in two patients (F7 and F8). The duration of infusion and dose adjustments are summarized in Table 1.

In most of our patients (F1–8 and M1–2), the total ropivacaine concentration increased after surgery until day 3. The individual peak total plasma concentrations (C_{max}) of all patients ranged between 2.39 and 6.08 µg ml^{-1}, with a mean (SD) of 4.1 (1.2) µg ml^{-1}. The average C_{max} was achieved at 67.7 (16.5) h. However, in two patients (F9 and M3), C_{max} was achieved after only a few hours of epidural infusion. Initially, a higher infusion rate was required for both patients because of high pain levels. Therefore the free and total plasma concentrations of ropivacaine were much higher than those in all other patients on the day of surgery. The necessary adjustments in infusion rates resulted in a decrease in ropivacaine plasma concentrations in both patients. The increase in ropivacaine concentrations until day 3 after surgery could have been concealed by these dose reductions.

In all patients, the unbound plasma concentration increased steeply during the initial 4 h of epidural ropivacaine infusion. The mean (SD) concentration of unbound ropivacaine was 0.039 (0.02) µg ml^{-1}. The

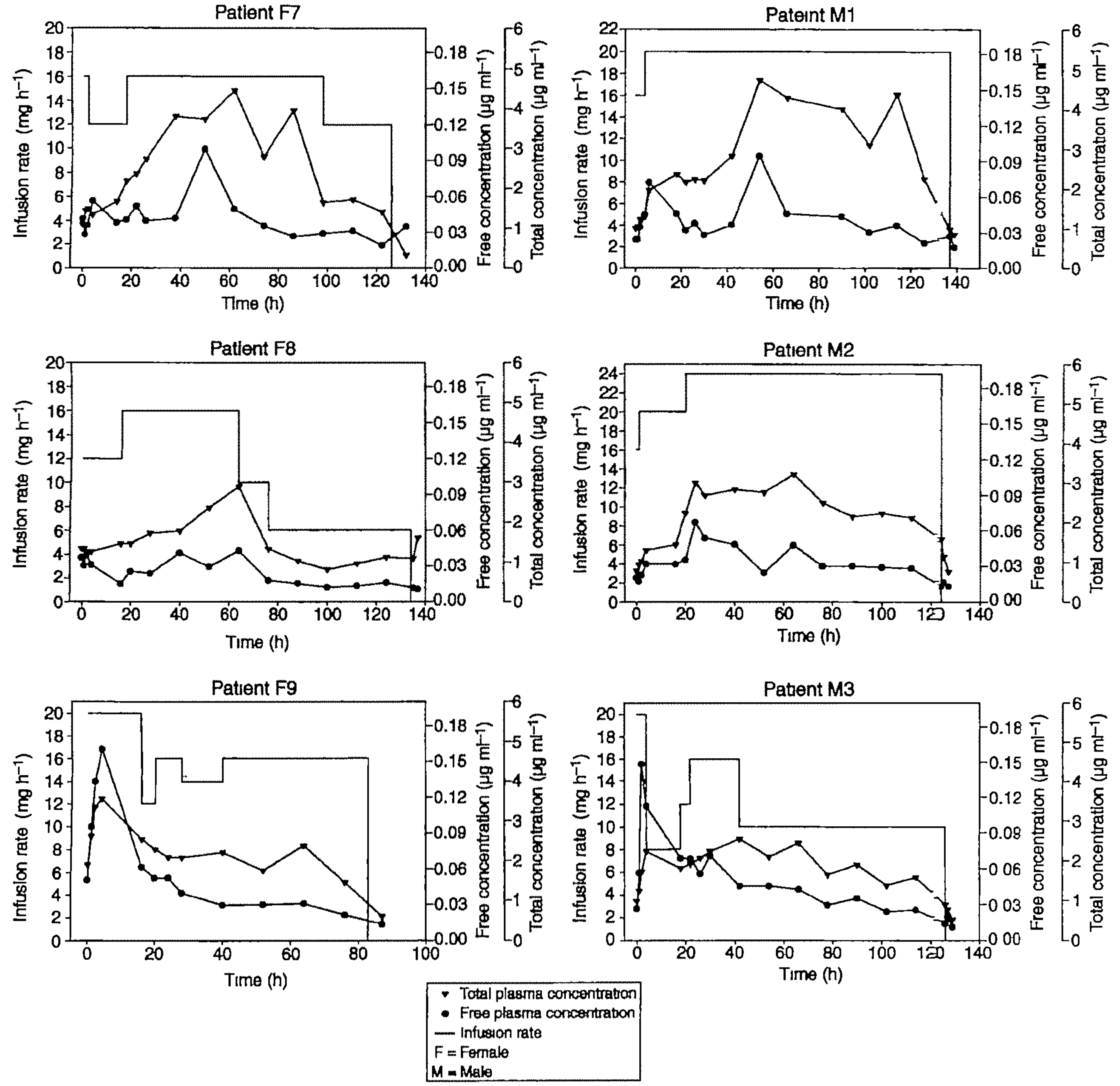

Fig 2 Individual time course of the total and free plasma concentration and the epidural infusion rate of ropivacaine using Naropin 2 mg ml^{-1}.

individual peak free plasma concentration was 0.096 (0.034) µg ml^{-1}. The highest free plasma concentration of ropivacaine (0.16 µg ml^{-1}) was noted in patient F9. The free plasma concentration decreased after approximately 70 h in all patients except patient F5, in whom the free concentration–time profile was stable over the 124 h infusion period. However, in this patient the total plasma concentration of ropivacaine increased throughout the observation period. The decrease in the total and free plasma concentrations of ropivacaine did not correlate with the infusion rate reduction except in patients F6 and F8. In accordance with the low free plasma concentrations, no signs of systemic toxicity were seen in the patients included in this study.

The AAG concentration (Fig. 3) decreased during the first 4–5 h of epidural infusion. Thereafter, it increased steadily throughout the 120 h follow-up period. The mean concentration of AAG had doubled by the end of infusion (1.55 (0.43) g litre^{-1}).

Discussion

This study was performed to evaluate the pharmacokinetics of ropivacaine during 120 h of CEDA. It is well known that

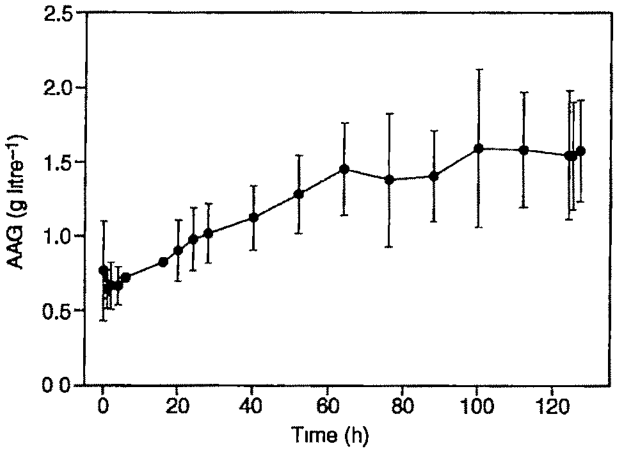

Fig 3 Variation of the mean(SD) plasma concentration of α_1-acid glycoprotein (AAG) with time

the toxic effects of local anaesthetics are more closely related to the free plasma concentration than to the total concentration, as only free drug can reach receptor sites.[19] As reported by Knudsen and colleagues,[4] the CNS toxicity threshold of free ropivacaine concentration is estimated to be between 0.34 and 0.85 $\mu g\ ml^{-1}$. However, this value is valid only for intravenous administration of ropivacaine. As explained by Santos and colleagues,[3] slower administration of ropivacaine will allow more extensive redistribution of the drug so that toxic manifestations may occur at higher doses but lower blood concentrations of drug.

In the present study, no evidence of free ropivacaine accumulation in plasma was observed. All free plasma ropivacaine concentrations were below the toxic level reported by Knudsen and colleagues.[4] The behaviour of the free ropivacaine concentration corresponds with previous observations.[12–15] Notably, we confirm the observation of Scott and colleagues[15] that the mean free ropivacaine concentration plateaus and decreases after approximately 70 h. This time course of the unbound drug could be due to variation in plasma protein binding.[20]

As shown in Fig. 2, after a minor decline immediately after surgery, the AAG concentration steadily increased. The initial dip in AAG concentration could have been caused by fluid replacement during the operation. This phenomenon has been reported after different types of surgery;[15 21] in both of these studies, initial reductions in plasma AAG concentration were associated with decreased plasma drug binding and therefore increased free fractions. The subsequent increase in plasma AAG concentration is probably related to surgical stress.[17 22] Our data suggest that the increase in AAG concentration after surgery is not inhibited by epidural analgesia. This is in accordance with results reported by Wulf and colleagues;[23] one possible explanation for this finding is that complete suppression of the stress response requires complete sympathetic and somatic blockade of the surgical site such as can be provided only with extensive epidural anaesthesia.[17]

The increase in total ropivacaine concentration up to 72 h has been observed before[15] and is thought to be caused by increased protein binding.[24 25] According to Burm,[26] the increasing total plasma concentration during the first 3 days reflects changes in plasma protein binding, related to increased AAG concentrations after surgery, so that increased total plasma concentrations are not accompanied by similar increases in the more important free drug concentration. These changes in plasma drug binding may have importance for the interpretation of total plasma drug concentrations. We found that the AAG concentration increased until the end of our observation period, in accordance with Wulf,[23] who reported that AAG concentration was maximal between 6 and 12 days after hip surgery.

The time course of the total ropivacaine concentration beyond 72 h has not yet been reported. Unexpectedly, we found that the total ropivacaine concentration began to decrease after approximately 68 h, and continued to decrease until the end of infusion. Thus would contradict the previous assumption that ropivacaine would probably accumulate in the plasma.[12–15] A 'steady state' total plasma concentration was not found, probably because it did not yet equilibrated. The decrease in the total plasma concentration may be have involved the major pathway of ropivacaine metabolism, by the P450 cytochromes CYP1A2 and CYP3A4.[27 28] Since chronic application of drugs that are metabolized by cytochrome P450, e.g. cocaine,[29] theophylline and midazolam,[30] can induce metabolism of cytochrome P450, it is possible that a similar phenomenon could be responsible for the decrease in the total and free plasma concentration of ropivacaine during chronic administration. Any other incidents interfering with ropivacaine metabolism can be excluded in our study.

We have shown that, during chronic administration of ropivacaine, the free plasma concentrations were well below the toxic concentration, emphasizing the safety and efficacy of long-term ropivacaine CEDA. The deductions that can be made from the results of our study are limited by the small number of patients. Further studies of long-term ropivacaine administration are needed.

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Pain management after adenoidectomy with ketoprofen: comparison of rectal and intravenous routes

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We compared the efficacy of rectally and intravenously administered ketoprofen for pain management after day-case adenoidectomy. Patients (123 children aged 1–9 yr) were allocated randomly to receive on induction of anaesthesia ketoprofen 25 mg rectally with an i.v. placebo, ketoprofen 25 mg i.v. with a rectal placebo, or placebo both i.v. and rectally. The method of anaesthesia and the operative technique were standardized. Postoperative pain was assessed at rest and during swallowing using the Maunuksela pain scale (0=no pain, 10=worst possible pain). Fentanyl 0.5 $\mu g\ kg^{-1}$ was given as rescue analgesia. There was no significant difference between the two ketoprofen groups in their requirement for rescue analgesics. However, both the proportion of children needing rescue analgesics [55 of 84 children (65%) *vs.* 33 of 39 children (84%); difference 19%, 95% confidence interval 4–34%, *P*=0.029] and the number of rescue analgesic doses [mean 1.2 (SD 1.2) *vs.* 2.2 (1.4); mean difference 0.9, 95% confidence interval 0.4–1.4, *P*=0.001] were significantly lower among children receiving ketoprofen than in children receiving placebo. Adverse events, duration of operation, perioperative bleeding, pain scores and time of discharge were similar in the three groups.

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Adenoidectomy is the most common day-case operation in children. Successful management provides a major challenge for the providers of health care and requires a multidisciplinary approach for the evaluation of quality. The criteria are minimal postoperative morbidity, low inpatient admission rate and high parental and child satisfaction.[1]

More than 50% of children undergoing day-case surgery experience clinically significant pain after discharge.[2 3] Furthermore, the pain experienced by the child in hospital after adenoidectomy predicts the behavioural problems and pain at home.[4 5] Non-opioid analgesics are effective in the treatment of mild and moderate pain in children.[6] Non-steroidal anti-inflammatory drugs (NSAIDs) not only produce good analgesia but also reduce the consumption of opioids and the incidence of adverse events, such as nausea and vomiting.[7] Ketoprofen is a derivative of propionic acid and is a commonly used NSAID in adults in many countries. The efficacy and safety of i.v. ketoprofen is also recognized in paediatric patients.[4 7]

During the perioperative period, oral analgesics may not be absorbed reliably, and therefore i.v. injection and rectal suppositories are used commonly. These routes of administration routes have not been compared adequately.[8] Therefore, the aim of this study was to evaluate whether rectal ketoprofen is as effective an analgesic as i.v. ketoprofen for pain management in children after day-case adenoidectomy.

Patients and methods

The study was approved by Ethics Committee of Kuopio University Hospital and was conducted in accordance with the Declaration of Helsinki. The National Agency for

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Medicines was notified of the use of ketoprofen in children weighing less than 20 kg. The parents and children who were old enough were informed about the study, and they provided written consent. Our study included 123 children (68 boys and 55 girls) aged 1–9 yr, ASA physical status I, who were undergoing day-case adenoidectomy during the autumn of 1999. Patients were excluded if they had known allergy to ketoprofen or other NSAIDs, asthma, haemorrhagic diathesis, kidney or liver dysfunction, or had any other known contraindication for NSAIDs.

A randomized, prospective, double-blind, double-dummy, placebo-controlled, parallel-group study design was used. Children were allocated randomly to either of the two ketoprofen groups or to a placebo group. The allocation was computer-generated and a sealed envelope method was used to ensure blinding. Forty-two children received ketoprofen rectally (suppository group), 42 children received ketoprofen i.v. (i.v. group), and 39 children received only placebo (placebo group).

In the suppository group, the children were given ketoprofen rectally 25 mg as a suppository (Ketorin® 25 mg supp., Orion, Espoo, Finland) after induction of anaesthesia but before surgery and placebo i.v. (0.9% normal saline 10 ml). In the i.v. group, the children were given a placebo suppository and ketoprofen 25 mg in 10 ml 0.9% normal saline i.v. injected over 5 min (Ketorin® 50 mg/ml injection, Orion). In the placebo group, the children were given a placebo suppository and an i.v. injection of normal saline. The buttocks were taped together after the insertion of the suppository to avoid displacement. After the operation we checked that the suppository had remained in the rectum. The injections were prepared by a nurse not taking part in the study, and the appearances of the ketoprofen and placebo suppositories were similar, thus ensuring blinding.

A standard anaesthetic technique was used. Each child was premedicated with diazepam 0.5 mg kg^{-1} orally up to a maximum of 10 mg 30 min before induction. EMLA® cream (Astra, Södertälje, Sweden) was used at the venous puncture site. Atropine 0.01 mg kg^{-1} was given i.v. and anaesthesia was induced with thiopental 5 mg kg^{-1} and fentanyl 1 μg kg^{-1} i.v. To facilitate tracheal intubation, *cis*-atracurium 0.1 mg kg^{-1} was given. Anaesthesia was maintained with 2–3% sevoflurane (inspired concentration) in 65% nitrous oxide in oxygen with intermittent positive-pressure ventilation. On completion of the procedure, muscle relaxation was reversed with neostigmine 50 μg kg^{-1} and glycopyrrolate 10 μg kg^{-1}. All children received fentanyl 1 μg kg^{-1} at induction, and no more opioids were allowed during surgery. For intraoperative fluid maintenance, all children were given 0.9% saline 5–10 ml kg^{-1} h^{-1}.

The adenoids were removed using a curettage technique under visual control. Haemostasis was by temporary nasopharyngeal packs and electrocautery. The operation time was recorded and, at the end of procedure, the surgeon estimated the amount of bleeding using a 5-point scale (0=no bleeding, 5=profuse bleeding).[4]

After surgery, the children were transferred to the postanaesthesia care unit (PACU), where vital signs were monitored and pain was assessed by specially trained nurses. Postoperative pain was assessed using the Maunuksela scale[9] as modified by Nikanne and colleagues (0=no pain, 10=worst pain).[4] Pain experienced by the child at rest and during swallowing was assessed continuously and recorded every hour up to 3 h. If the child was in pain with a pain score at rest ⩾3, fentanyl 0.5 μg kg^{-1} i.v. was given. The dose was repeated at 5 min intervals until the pain had diminished to a rating of 'slight'. No more than four doses were allowed in any period of 1 h. No other analgesic medication was permitted during the study. The last pain assessment and recording was made just before discharge. At the same time, the worst pain during the patient's stay in the PACU was noted. At discharge, sedation was assessed using a 100 mm visual analogue scale (VAS, left end=full alert, right end=not arousable). All adverse effects were recorded for each patient.

Patients were discharged when they were awake, were able to walk unaided, had had stable vital signs for at least 1 h, had no pain or only mild pain, had not vomited for 1 h, were able to tolerate clear fluid, and had no bleeding. All children received ketoprofen 1 mg kg^{-1} i.v. just before discharge. The discharge was defined as delayed if it was later than 5 h after surgery.

The sample size was based on detecting a difference of 35% or more in the need for rescue analgesic between the i.v. and suppository groups at a significance level of 0.05 with 80% power. Continuous variables were analysed with the Kruskal–Wallis test, and for *post hoc* analysis the Mann–Whitney test with Bonferonni correction was used. For the categorical variables, the χ^2 test was used. $P<0.05$ was considered statistically significant. Results are presented as number of cases (%), median (10th and 90th percentiles), mean (SD) or mean difference [95% confidence interval (CI)] as appropriate.

Results

The three groups were similar in age, weight and height. In the i.v. group there were more boys than in the two other groups ($P=0.017$, χ^2 test) (Table 1). There were no protocol deviations or exclusions.

The number of rescue analgesic doses needed in the study groups is presented in Fig 1. There was no difference between the two ketoprofen groups in the need for rescue analgesia; in the suppository group 27 out of 42 children (64%) and in the i.v. group 28 out of 42 children (67%) received rescue analgesia in the PACU. In the placebo group 33 out of 39 children (85%) needed rescue analgesia in the PACU; the difference with respect to the children receiving ketoprofen was significant (i.v./suppository groups *vs*

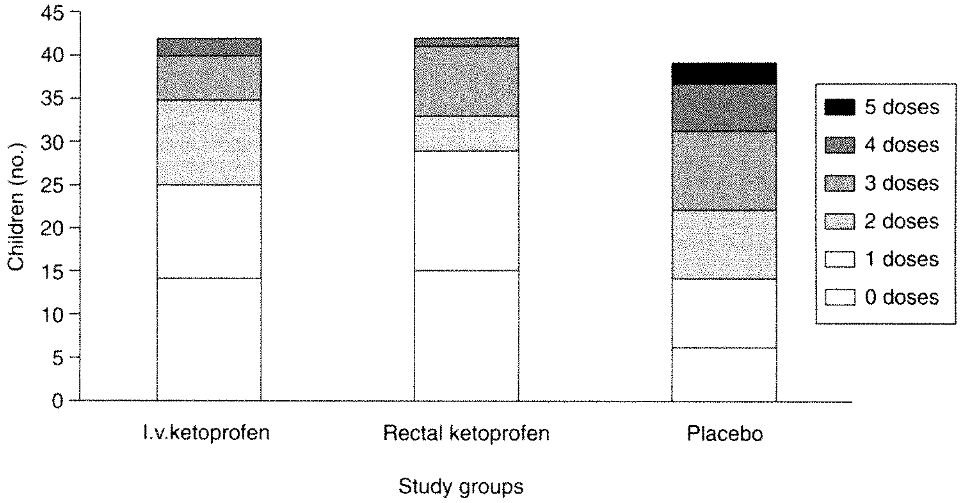

Fig 1 Use of rescue analgesics.

placebo group: difference 19%, 95% CI 4–34%, P=0.029, χ^2 test).

The number of rescue analgesic doses needed in the PACU was significantly smaller in children receiving ketoprofen than in children receiving placebo (P=0.004 compared with the suppository group, P=0.012 compared with the i.v. group; Mann–Whitney test with Bonferonni correction). There was no difference between the two ketoprofen groups.

For the 88 children who needed rescue analgesics in the PACU, ketoprofen significantly reduced the number of doses of rescue analgesia compared with the placebo group (P=0.038, Kruskal–Wallis test). There was no difference between the two ketoprofen groups.

Of the children who needed rescue analgesics in the PACU, seven out of 28 (25%) in the i.v. group needed three or more doses of rescue analgesics compared with nine out of 27 (33%) in the suppository group; the difference was not significant. In the placebo group, significantly more children [17 out of 33 (52%)] needed three or more doses of rescue analgesia compared with children receiving ketoprofen (i.v./suppository groups *vs* placebo group: difference 22%, 95% CI 2–45%, P=0.015, χ^2 test).

Although the median time to the first fentanyl dose was 23 min (10th and 90th percentiles, 5 and 105 min) in the placebo group compared with 35 (10 and 100) min in the suppository group and 32 (5–90) min in the i.v. group, the differences were not significant.

There was no significant difference between the study groups in their Maunuksela pain scores during the PACU stay or at discharge. Sedation at discharge was also similar (Table 2). There were no differences between the study groups in the amount of intraoperative bleeding evaluated by the surgeon (Table 3). No children experienced postoperative bleeding that required further surgery, delay in discharge, admission to hospital or any other intervention.

Table 1 Patient characteristics. Age, height and weight are given as median (10th and 90th percentiles). *P=0.017

	I.v. ketoprofen (n=42)	**Rectal ketoprofen (n=42)**	**Placebo (n=39)**
Male/female (n)	30/12*	17/25	21/18
Age (months)	44 (15, 97)	33 (17, 90)	45 (14, 73)
Height (cm)	100 (79, 136)	93 (80, 128)	105 (78, 119)
Weight (kg)	15 (11, 30)	14 (12, 27)	18 (11, 25)

Table 2 Maunuksela pain scores (0=no pain, 1–3=slight pain, 4–6=moderate pain, 7–9=severe pain, 10=worst possible pain). Data are medians (10th and 90th percentiles)

	I.v. ketoprofen (n=42)	**Rectal ketoprofen (n=42)**	**Placebo (n=39)**
Pain at 1 h			
At rest	5 (0, 7)	4 (0, 8)	6 (0, 8)
During swallowing	5 (0, 8)	4 (0, 8)	7 (1, 8)
Pain at 2 h			
At rest	0 (0, 5)	0 (0, 2)	1 (0, 5)
During swallowing	1 (0, 5)	1 (0, 4)	2 (0, 5)
Worst pain in PACU			
At rest	4 (0, 8)	4 (1, 8)	5 (0, 8)
During swallowing	5 (1–8)	5 (1–8)	6 (1–8)
Pain at discharge			
At rest	0 (0, 1)	0 (0, 1)	0 (0, 1)
During swallowing	0 (0, 2)	0 (0, 2)	1 (0, 2)

There were no differences between the study groups in the incidence of adverse events (Table 4). The most common adverse events were nausea, retching and vomiting [16 out of 123 children (13%)]. Anorectal adverse events did not occur.

Discharge was delayed in four out of 42 children (10%) in the i.v. group, three out of 42 children (7%) in the suppository group and one child (3%) in the placebo

Table 3 Amount of intraoperative bleeding assessed by the surgeon. Data are numbers of cases

	I.v. ketoprofen (n=42)	Rectal ketoprofen (n=42)	Placebo (n=39)
Less than normal	2	5	1
Normal	38	34	37
More than normal	2	3	1

Table 4 Adverse events. Data are numbers of cases

	I.v. ketoprofen (n=42)	Rectal ketoprofen (n=42)	Placebo (n= 39)
Nausea, retching, vomiting	5	6	5
Pain at infusion site	–	–	2
Difficulty in passing urine	1	–	–
Somnolence	1	3	–
Agitation	1	–	–
Number of children with adverse events	6	6	7

group, because of severe pain, protracted vomiting or excessive sedation. Seven children were discharged after 6 or 7 h. One child in the suppository group was admitted to hospital because of protracted vomiting. Her recovery was uneventful and she was discharged on the first postoperative morning.

Discussion

In this study, rectally administered ketoprofen was as effective as i.v. ketoprofen. There was no significant difference between the two ketoprofen groups in the number of children requiring rescue analgesia or in the number of rescue analgesic doses needed. However, compared with placebo, ketoprofen was significantly more effective. Overall, 65% of children needed rescue analgesia in the ketoprofen groups, whereas in the placebo group 85% of children needed rescue analgesia. This supports our earlier results, which showed that ketoprofen is a safe and effective non-opioid analgesic in children.[4 7]

A study in adults showed that 73–93% of ketoprofen is absorbed after administration of a rectal suppository.[10] However, drug absorption after rectal administration in children may be delayed and erratic, as shown with paracetamol.[11] We believe that one reason for unpredictable absorption could be evacuation of the suppository from the rectum as a result of the defaecation reflex caused by insertion of the suppository. In this study, the problem was avoided by taping the buttocks together after insertion of the suppository. When checked after surgery, none of the suppositories had come out.

Guidelines of the Royal Colleges of Surgeons of England suggest that day cases managed in a dedicated unit should have an inpatient admission rate of no higher than 2 or 3%. In this study, only one child was admitted and discharge was delayed in only eight children. One child had difficulty in passing urine, five children had protracted nausea and vomiting and two children in the placebo group had severe pain. Chung and Mezei evaluated factors predicting a prolonged stay after day-case surgery and found that excessive pain and protracted nausea and vomiting are the most significant factors.[12] The overall rate of delayed discharge of 6% in this study was much higher than we have observed in our previous studies.[4 7] Normally, day cases recover within a dedicated day-case recovery area but, because of maintenance work, children in this study recovered in the main inpatient recovery ward. We believe that this may explain our high rate of delayed discharge.

Volatile anaesthetics, for example sevoflurane, are common agents for the maintenance of anaesthesia. Sevoflurane allows easy control of the depth of anaesthesia and rapid recovery characteristics, but has been associated with recovery agitation.[13] There is increasing evidence that sevoflurane must be combined with an analgesic. Katoh and colleagues showed recently that the use of fentanyl significantly reduced the requirement of sevoflurane.[14] Moreover, Davis and colleagues showed that intraoperatively administered NSAID reduced agitation on emergence from anaesthesia.[15] The effect of ketoprofen on the need for sevoflurane has not been determined. Since ketoprofen also has a central analgesic effect, it would be interesting to evaluate the interaction between sevoflurane and ketoprofen.[16]

Rectal administration is used in some countries but, in most cases, the principal reason for choosing the rectal route is based on tradition. In Finland, awake children dislike suppositories.[17] Our results show that, during anaesthesia, rectally administrated ketoprofen is an effective alternative to i.v. administration.

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Sonographic measurement of needle insertion depth in paravertebral blocks in women

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Single-injection paravertebral block offers adequate unilateral analgesia for thoracic and upper abdominal surgery. This technique is easy to learn but there is a risk, albeit low, of pleural puncture. The aim of the study was to determine whether sonographic measurements of the distances from the skin to the transverse process and to the parietal pleura are useful for calculating the required depth of needle insertion. Before puncture of the paravertebral space, the distances from the skin to the transverse process and to the parietal pleura were measured by sonography. The deviation of the needle from the horizontal plane was measured and an angle correction for the insertion depth was calculated. Twenty-two women undergoing elective unilateral breast surgery were studied. Sonographic visualization of the transverse process and the parietal pleura and measurement of their distances from the skin was successful in all women. Puncture of the paravertebral space failed in one obese woman. There was a very close correlation between needle insertion depth from the skin to the transverse process and the distance measured by ultrasound if angle correction was used (adjusted r^2=0.95). Similarly, there was excellent correlation between the angle-corrected ultrasound distance from the skin to the parietal pleura and the distance from the skin to the paravertebral space (adjusted r^2=0.92).

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Single-injection paravertebral block offers excellent intraoperative analgesia, reduces analgesia requirements after surgery and decreases discomfort after breast surgery.[1] To minimize the risk of pleural puncture, accurate placement of the needle in the paravertebral space, as recognized by the loss of resistance technique, is essential.[2] Accurate knowledge of the depth of the paravertebral block and the maximum needle insertion depth that would avoid pleural puncture would make it easier to perform paravertebral block. The purpose of the study was to determine whether ultrasound scanning of the transverse process and the parietal pleura can give an accurate reading of the depth to the paravertebral space.

Methods

After Institutional Review Board approval and written informed consent, 22 women (ASA I–II) undergoing unilateral elective breast surgery were included in the study. All women were scheduled for single-injection paravertebral block at the level of T4.[1] Patients were followed up for ≥12 h, in the PACU for the first 4 h and on the general ward later. Exclusion criteria were: age >70 yr, allergy to local anaesthetics, coagulation disorders and local infection at the injection site.

After application of standard monitoring, including ECG, non-invasive arterial pressure and pulse oximetry, all patients were sedated with midazolam 1–3 mg iv Women were placed on their side, with the side to be blocked uppermost, and were scanned with a Hewlett–Packard scanner with a 7.5 MHz linear array probe. The transverse process was located and its distance from the skin and the distance of the parietal pleura from the skin were determined. The scanning head was placed at 90° to the skin in all planes, 3.5 cm from the anatomical midline at the level of the cephalad end of the spinous process of T4. The

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Table 1 Patients and surgical characteristics (mean (range) unless otherwise stated)

Age (years)	57 7 (46–75)
Height (cm)	163.2 (150–171)
Weight (kg)	71.2 (47–98)
Type of surgery (*n*)	
Lumpectomy	9
Lumpectomy + axillar dissection	10
Mastectomy	1
Mastectomy + axillar dissection	1

Table 2 Mean (range) distances, in mm, from the skin to anatomical landmarks and angle deviation of the needle from the vertical plane in degrees, LOR=loss of resistance

Skin to transverse process (ultrasound)	21 (9–34)
Skin to parietal pleura (ultrasound)	35 (24–52)
Skin to bony contact (needle)	25 (15–38)
Angle of needle deviation to bony contact	8 (0–25)
Skin to LOR using needle	40 (24–56)
Angle of needle deviation to LOR	35 (20–50)
Expected distance from skin to parietal pleura	44 (26–59)

transverse process and the parietal pleura were located by ultrasonography.

The skin was sterilized and then it and underlying structures were locally infiltrated with 3 ml of 2% lidocaine. The needle used for infiltration was inserted at 90° to the skin in all planes to strike the transverse process; the distance from the skin to the bony contact was marked on the needle and subsequently measured with a ruler. Angle corrections, if required to reach the bony contact, were recorded. Paravertebral block was performed 3.5 cm from the anatomical midline, as proposed by Eason and Wyatt.[3] A 22 gauge spinal needle (Terumo spinal needle; Terumo Corporation, Tokyo, Japan) was inserted 3.5 cm from the anatomical midline at the level of the cephalad end of the spinous process of T4. The needle was advanced at 90° to the skin in all planes to strike the transverse process or the head of the rib. It was then directed over the top of the bony structure. The technique of loss of resistance to normal saline injection was used to identify the paravertebral space after the needle passed the costotransverse ligament. The depth was marked on the needle and the distance was measured with a ruler. After negative aspiration, a test dose of 5 ml of 0.5% bupivacaine with 1:200 000 epinephrine was administered incrementally. A single injection of 0.3 ml of 0.5% bupivacaine kg^{-1} (maximum dose 150 mg) with 1:200 000 epinephrine was performed in all patients. The duration of injection of the local anaesthetic was $\geqslant$120 s. The puncture of the paravertebral space was performed in all cases by the same anaesthetist, who was blinded to the results of the ultrasonographic measurements. The patient's body position was unchanged from the beginning of the ultrasonographic measurements until the block was finished. The angle deviation of the needle from the horizontal line was noted in order to calculate the angle correction of the sonographic distance: (i.e. needle distance=sonographic distance/cosine angle deviation). Angle deviation was measured with a protractor held on the patient's skin.

The pinprick method and thermographic spread were used to assess the extent of analgesia. Paravertebral blocks with a thermographic spread (sympathetic block) of <4 dermatomes or loss of pinprick sensation of <3 dermatomes were taken to indicate incorrect puncture. Ipsilateral warming was recorded using an infrared temperature scanner (Dermatemp, Exergen, Watertown, MA, USA). Patients with insufficient paravertebral block were excluded from study evaluation. A chest X-ray was performed in all patients after surgery to exclude pleural puncture.

Patients characteristics and all distances are presented as mean (range). Correlations were calculated by the Spearman rank test.

Results

Twenty-two women undergoing elective unilateral breast surgery were studied and 21 finally evaluated. In one obese woman, puncture of the paravertebral space was abandoned because of inability to identify the paravertebral space, whilst sonographic measurements were successful. No other patient was excluded. The characteristics of the remaining 21 patients are presented in Table 1. Sonographic visualization of the key structures (parietal pleura and transverse process) and paravertebral block were successful in all women.

There was a very close correlation between the distance of the needle from the skin to the transverse process and the distance measured by ultrasound if angle correction was used (adjusted r^2=0.95). The distance measured by ultrasound difference was always less than the needle distance, the mean difference being 4 mm (range 1–7 mm). Similarly, the angle-corrected ultrasound distance from the skin to the parietal pleura showed excellent correlation with the needle distance from the skin to the paravertebral space (adjusted r^2=0.92). Again, the ultrasound distance always exceeded the needle distance, the mean difference being 4 mm (range 1–7 mm). In all women, the angle-corrected sonographic distance from the skin to the pleura was greater than the distance of the needle from the skin to the paravertebral space. No accidental pleural puncture occurred in our study.

Discussion

Ultrasound scanning of the transverse process and the parietal pleura gave an accurate reading of the depth to the paravertebral space, helping to avoid accidental pleural puncture. Sonographic measurements correlated well with distances found during needle insertion when angle correction was used. The maximum insertion depth required to minimize the risk of pneumothorax could be predicted accurately.

Although accidental pleural puncture is rare,[2] paravertebral block is still considered potentially dangerous by many anaesthetists,[4] so the technique is performed infrequently. However, some centres specialized in this block consider it the regional anaesthesia of choice for unilateral thoracic or abdominal surgery.[4] Using ultrasound to visualize anatomical landmarks, it may be possible to improve the safety of the block.

The transverse process is an important landmark when one is performing paravertebral block. However, it can be difficult to locate in obese patients or in cases of vertebral abnormality, so the risk of pleural puncture may be higher in these patients. The finding that the apparent distances from the skin to the bony contact when measured using the needle method were greater than angle-corrected sonographic measurements may be explained by tangential contact of the transverse process or by skin compression with the scanning head. This compression might in part explain the relatively small differences between the distance to the paravertebral space and the angle-corrected ultrasound distance to the parietal pleura. Another explanation could be the quite lateral approach to the wedge-shaped paravertebral space of 3.5 cm laterally from the anatomical midline.

Ultrasound scanning of the transverse process and the parietal pleura provides accurate assessment of the maximum needle insertion depth to avoid pleural puncture and enables calculation of the depth to the paravertebral space. Prior knowledge of the depth to the paravertebral space should make paravertebral block easier to perform.

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Weal and flare responses to intradermal rocuronium and cisatracurium in humans[†]

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Thirty volunteers underwent intradermal skin testing with increasing concentrations of rocuronium and cisatracurium to evaluate weal and flare responses, and whether either agent would cause mast cell degranulation and sensitization upon re-exposure. We found that intradermal injection of rocuronium and cisatracurium at concentrations $>10^{-4}$ M resulted in positive weal (>8 mm) responses, and positive flare responses at $>10^{-4}$ and $>10^{-5}$ M respectively. Only cisatracurium caused mild to moderate mast cell degranulation, and neither drug caused significant *in vitro* histamine release from whole blood collected from study subjects 4 weeks after skin testing. Skin testing with rocuronium and cisatracurium should be performed at concentrations $<10^{-4}$ and $<10^{-5}$ M respectively to avoid false-positive responses. The ability of these agents to produce positive weal and flare responses at relatively low concentrations may explain the high incidence of potential reactions reported.

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Many agents administered in the perioperative period have the potential to produce allergic reactions upon re-exposure.[1 2] However, certain drugs may directly affect inflammatory cells and the vascular system to produce adverse reactions that are often falsely labelled as allergic. Drugs that directly release histamine from mast cells can also confound tests that use the skin as an immunological window to assess patients with the potential for allergic reactions. Opioids, neuromuscular blocking agents (NMBAs) and some other drugs (e.g. vancomycin, aprotinin and protamine) are highly charged molecules that have the ability to produce positive weal and flare responses independently of mast cell degranulation.[3–5] Steroid-derived NMBAs also have direct vasodilating effects.[6] These false-positive cutaneous responses can confuse allergy testing and interpretation, especially when different concentrations of the same drug(s) are used for testing by various investigators.[7–9] Unfortunately, the actual threshold concentrations for skin testing have not been determined for the newer neuromuscular blocking drugs. Further, previous reports of perioperative anaphylaxis in France have implicated steroid-derived agents (i.e. rocuronium and vecuronium) as the offending drugs, based on positive results of skin testing.[7] We investigated the effects of intradermal injections of increasing concentrations of neuromuscular blocking drugs on weal and flare responses in order to determine the threshold for allergic sensitization and to develop a guideline for using the appropriate concentrations of neuromuscular blocking drugs when skin-testing subjects. We also performed leukocyte histamine release tests using whole blood collected from each volunteer to determine their potential for sensitization.

Methods

Thirty healthy volunteers were recruited for the study after institutional approval and informed consent. Subjects were excluded if they had a history of anaphylaxis or asthma or were taking steroid medications, antihistamines or H_1 or H_2 blockers. All subjects received all doses of rocuronium first, followed by all doses of cisatracurium besylate. The control substances—saline (negative control), atracurium besylate (positive control) and histamine (positive control)—were administered to all subjects. Rocuronium was used as a preservative-free 10 mg ml^{-1} solution. Cisatracurium besylate was supplied as a marketed product in 20 ml

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vials, which contain 10 mg ml^{-1} solution ready for injection. Atracurium besylate was supplied in 5 ml vials containing atracurium besylate 50 mg in solution (10 mg ml^{-1}) ready for injection. Histamine phosphate was supplied in 5 ml vials which contained 2.75 mg ml $^{-1}$ solution ready for injection. Saline was supplied in 2 ml vials at 0.9% NaCl. All drugs were diluted with 0.9% saline to obtain appropriate dilutions ready for testing.

Each subject underwent intradermal skin testing (during the first visit only) with the following study medications (using 0.02 ml injections): rocuronium 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2} M; cisatracurium besylate 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2} M; 0.9% normal saline solution; atracurium besylate 10^{-4} M; and histamine 10^{-4} M. All study drugs were injected intradermally through a $28\frac{1}{2}$ gauge needle into the right and left forearms of each subject. In order to avoid confusion with the injections and the data collection during the study, the first study drug (rocuronium) was administered in all dilutions to the lateral part of the right forearm followed by the second study drug treatment (cisatracurium besylate) in all dilutions on the medial part of the same arm. The controls—saline (negative), atracurium besylate (positive) and histamine (positive)—were administered on the left forearm. All solutions were freshly prepared and were preservative-free. After 10–15 min, the sizes (diameter in mm) of the weals and flares were evaluated by an assessor who was blinded to the study drugs (the assessor was not present when the injections were made and did not know the order of the drugs injected). A weal was defined as a smooth, elevated area on the skin surface, often redder or paler than the surrounding skin. Positivity was shown by a pale pink weal with a diameter greater than 8 mm. A flare was defined by the red outermost zone of the weal reaction. The two largest diameters of the weals and flares were recorded and the diameters averaged. Punch biopsies from the drug-induced weals were taken during the first testing from six of the 30 subjects who had a positive response (weal $\geqslant$8 mm in diameter or $\geqslant$75% of the diameter of the histamine control weal). If a subject had more than one positive response to the study drug(s), the weal produced by the lowest concentration of the study drug(s) that induced a positive weal response was biopsied. Biopsies of the sites of saline control treatments were also taken from the same subjects. The physician performing the punch biopsies was blinded to the study drugs and the corresponding concentrations that gave positive responses.

A 3 mm punch biopsy specimen was taken after injecting lignocaine without preservative around the site to be biopsied using deep subcutaneous injection. The skin specimens were cut into 1.5 mm pieces and immediately placed in fixative solution for light microscopy, or immersed in Karnofsky's fixative and processed for transmission electron microscopy. After processing, semi-thin sections were cut and stained with Giemsa for light microscopy. These were examined for degranulation and to select areas with mast cells for thin sectioning. Thin sections (70.0 nm) were cut and counterstained with lead citrate and uranyl acetate. An assessor who was blinded to the study medications examined these specimens under a Phillips 201 electron microscope. The presence of degranulation, the mast cell morphology, granule architecture and comments on the histology were recorded. Degranulation was recorded as 0, 1+, 2+, 3+ or 4+, where 0 represents normal mast cell morphology without evidence of degranulation and 4+ represents complete degranulation.

Blood samples for *in vitro* histamine release were collected from each subject at the screening visit, before intradermal drug administration and at the follow-up visit 4 weeks after skin testing. For each subject, 10 ml of venous blood was collected into a vacutainer tube containing sodium heparin. Whole blood was diluted (1:5) with the releasing buffer (supplied as a part of the immunoassay kit used for histamine determination; Beckman-Coulter, Miami, Florida, USA). The potential for rocuronium and cisatracurium to mediate allergic sensitization was assessed by adding predetermined concentrations of either drug to separate plastic tubes containing 200 µl of diluted whole blood preparation and 100 µl of releasing agent. The rocuronium (2.5×10^{-5} M) and cisatracurium besylate (4×10^{-6} M) concentrations were chosen to correspond to the blood levels that would be seen clinically. The calcium ionophore A23187 (3.33×10^{-5} M; Sigma Chemical, St Louis, MI, USA) and anti-IgE (Sigma Chemical) were used as positive controls. Negative control tubes (baseline release) had only diluted whole blood and buffer added to the tubes (no drugs). The tubes were incubated in a shaking water bath for 30 min at 37°C. At the end of the incubation, the tubes were immediately placed on ice and then centrifuged for 10 min at 900 *g* at 4°C. The supernatant was separated and stored at –70°C until analysed. For total histamine determination, 50 µl of undiluted blood was added to 950 µl of distilled water (1:20 dilution), frozen, and thawed three times in order to lyse the cells. The sensitivity of the method allows histamine quantitation down to 0.5 nM (0.05 ng ml^{-1}).

The percentage of histamine release from 1 ml of blood by buffer, anti-IgE, calcium ionophore, rocuronium and cisatracurium besylate treatments was calculated using the formula: $100\times D/T=\%$ histamine release, where D=concentration of histamine in the sample containing the drug/buffer and T=total concentration of histamine in the frozen and thawed sample.

The Wilcoxon signed-rank test was used to compare the percentage of positive reactions with the percentage in the control (saline) group. A paired Student's *t*-test was used to compare mean weal and flare diameters with the mean for the saline control. Student's *t*-test was used to compare mean percentage histamine release for rocuronium and cisatracurium between the first visit and the follow-up and with the mean percentage histamine release for the positive

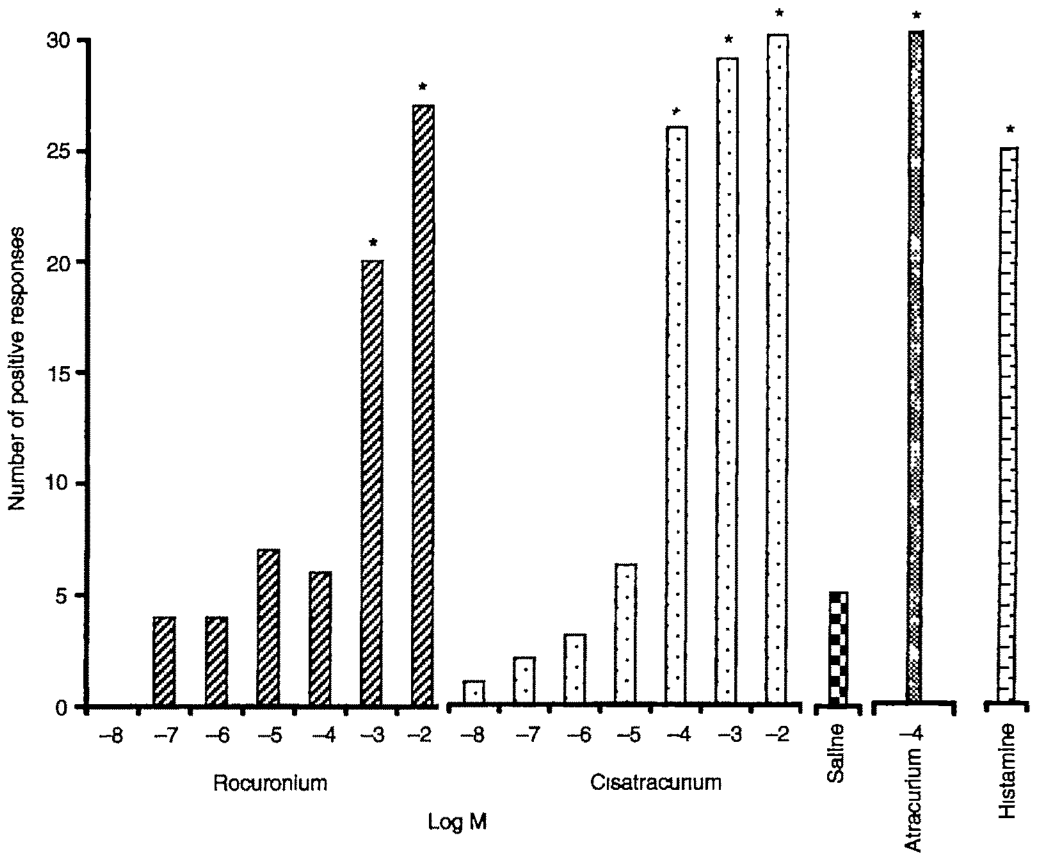

Fig 1 Number of subjects with positive responses to increasing concentrations of rocuronium, cisatracurium and to positive and negative controls (n=30). *P<0.05 *vs.* saline control.

control. In all tests $P \leq 0.05$ was considered statistically significant. All data are expressed as mean (SE).

Results

Data for the subjects with positive cutaneous reactions are shown in Figs 1–3. Rocuronium produced positive weal responses in 27 volunteers and positive flare responses in 29 volunteers at concentrations $>10^{-4}$ M, and 20 out of 30 patients had positive cutaneous reactions at 10^{-3} M (P<0.05). Cisatracurium produced positive weal responses at $\geq 10^{-4}$ M and positive flare responses at $>10^{-5}$ M in all volunteers, and 25 out of 30 volunteers had positive cutaneous responses at 10^{-4} M (P<0.05). There was no evidence that allergy to either rocuronium or cisatracurium had developed *de novo* (P<0.001) in 29 volunteers 4 weeks after skin testing compared with positive controls (anti-IgE and calcium ionophore). One subject in the follow-up did not return for testing. There were no differences in mean percentage histamine release for rocuronium (P=0.22) or cisatracurium (P=0.34) between the initial and follow-up visits.

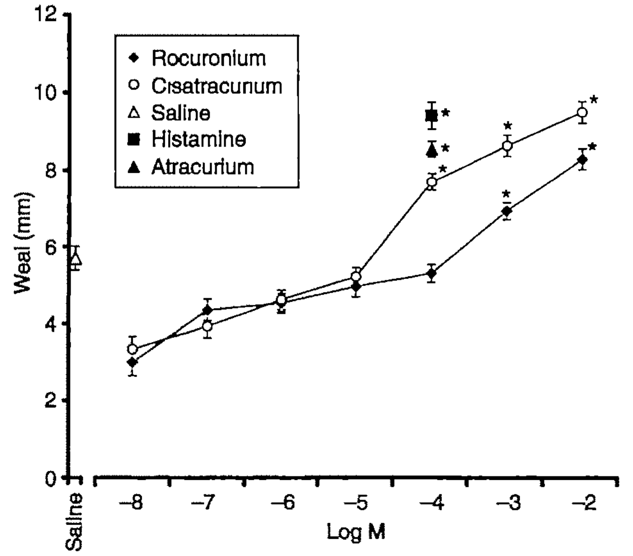

Fig 2 Weal sizes (mean and SE) after intradermal injection of normal saline, atracurium 10^{-4} M, histamine 10^{-4} M and increasing concentrations of rocuronium and cisatracurium *P<0.05 *vs.* saline control

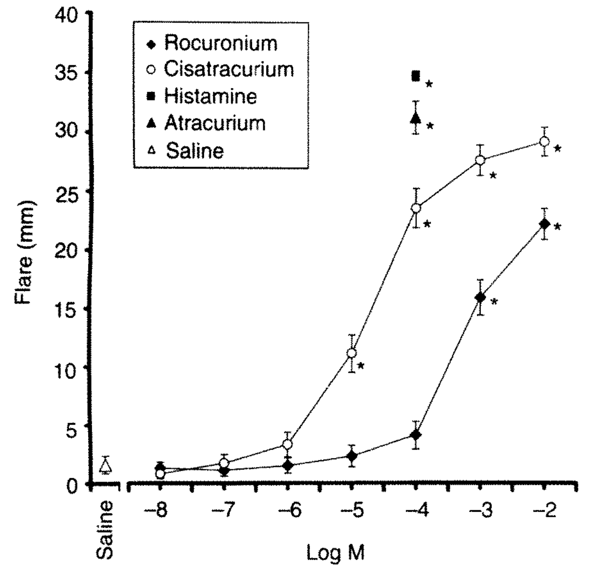

Fig 3 Flare sizes (mean and SE) after intradermal injection of normal saline, atracurium 10^{-4} M, histamine 10^{-4} M and increasing concentrations of rocuronium and cisatracurium. $*P<0.05$ *vs.* saline control.

Light and electron microscopy of the skin biopsies of saline and rocuronium weals revealed normal mast cell morphology without evidence of degranulation, and mild to moderate degranulation in the cisatracurium induced weals (Figs 4A and B).

Discussion

Our findings suggest that skin testing for hypersensitivity reactions to rocuronium should be performed with concentrations $<10^{-4}$ M. As rocuronium is prepared as a 10 mg ml^{-1} solution that is approximately 10^{-2} M, rocuronium needs to be diluted at least 100-fold before skin testing to prevent false-positive skin tests. This is important because the high incidence of positive cutaneous responses to rocuronium reported in France occurred in patients who were skin-tested with 1:10 dilutions of stock rocuronium solution (approximately 10^{-3} M) and may represent false-positive skin tests.[7] Bouaziz and Laxenaire suggest that rocuronium used at 1:10 dilution (1000 μg ml^{-1}) for intradermal skin testing in controls will not produce any cutaneous reaction.[8] According to the information pamphlet published by the Commission Tripartite de Consensus en Allergologie, skin testing for atracurium and mivacurium hypersensitivity should not be done with drug dilutions less than 1:1000 because of the possibility of false-positive reactions with more concentrated solutions (lower dilutions), but dilution can proceed down to 1:10 with rocuronium.[9] This is in direct contrast to our data. We noted that 66% of volunteers in our study had positive skin tests (Fig. 1) when injected with rocuronium solution diluted approximately 10-fold (i.e. 1:10 dilution). Light and electron microscopy of positive test biopsies showed no evidence of mast cell degranulation, further supporting the evidence for false-positive weal and flare responses. In recently published reports describing acute reactions to rocuronium, intradermal testing was done at 1:10 dilution,[10] and for prick-testing rocuronium was diluted 1:10 and 1:100[11] We believe that the use of drug concentrations higher than those used in our study may have led to the false-positive results. Additional prick-testing studies are needed to determine the optimal concentrations of NMBAs to be used during allergy testing in order to minimize false-positive reactions.

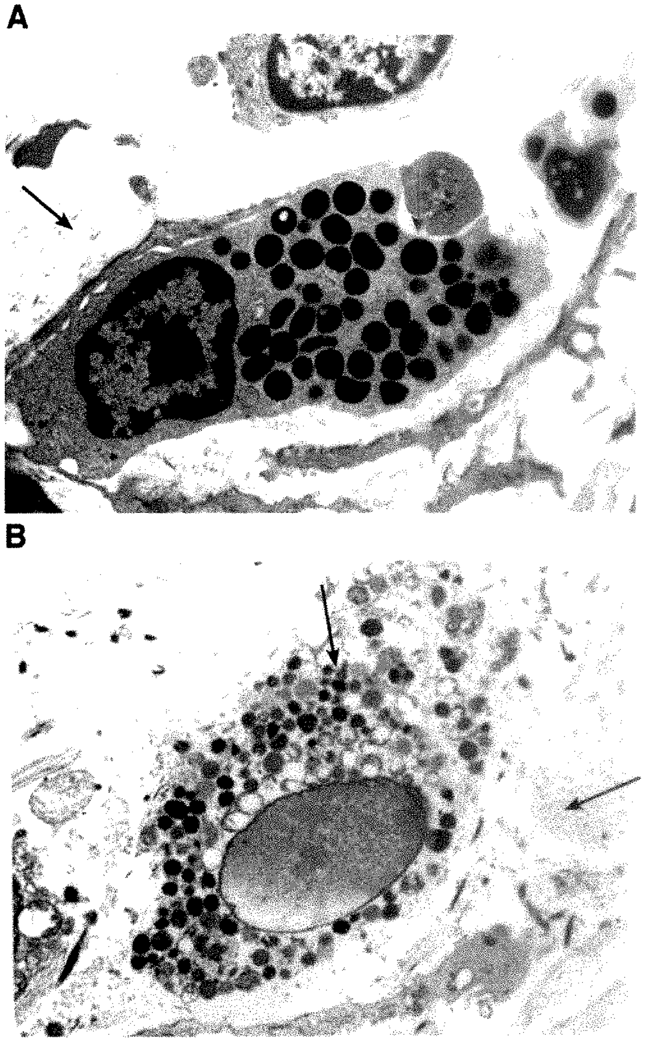

Fig 4 (A) Electron micrograph of a human cutaneous mast cell from a rocuronium-induced wheal. The cell outline is well defined, and the electron-dense cytoplasmic granules that store mast cell mediators are well delineated (arrow), without any evidence of degranulation. Note the collagen bundles around the mast cell (arrow). (B) Electron micrograph of a human cutaneous mast cell from a cisatracurium-induced wheal. Most of the cytoplasmic granules are swollen, and demonstrate varying degrees of decreased density and loss of organization consistent with ongoing degranulation (arrow). Note the collagen bundles around the mast cell (arrow).

When patients are skin-tested with cisatracurium, solutions should be diluted to $<10^{-5}$ M, approximately a 1000-fold dilution (based on 10 mg ml^{-1} of stock solution ~10^{-2}

M). We also noted that cisatracurium produced mast cell degranulation at a local level, as evidenced by light and electron microscopy (Fig. 4B). Further, because previous reports have suggested the threshold for non-immunological degranulation with neuromuscular blocking drugs is approximately 10^{-5} M,[3 5] cisatracurium produces positive weal and flare responses at the thresholds previously reported with other benzylisoquinoline-derived agents.[3 5] Why cisatracurium, another benzylisoquinoline-derived agent, does not release histamine in clinical studies may be a reflection of its potency and the smaller amount of drug administered.

There was no evidence that allergy to either rocuronium or cisatracurium developed *de novo* in the 29 volunteers studied, as evidenced by the lack of histamine release in blood samples collected at the follow-up visit and in comparison with the response elicited by anti-IgE or calcium ionophore, which were used as positive controls. Despite the small numbers of patients studied, this is an important finding because of the potential for anaphylaxis during re-exposure to NMBAs.[12] Monneret and colleagues suggest that, in some cases, detecting basophil activation by flow cytometry may be a useful additional test, helpful in detecting the identity of the offending agent.[10] Additional studies will be needed to validate the use of flow cytometry in allergy testing. NMBAs have several unique molecular features that make them potential allergens. All neuromuscular blocking drugs are functionally divalent, which makes them capable of cross-linking cell-surface IgE and initiating mediator release from mast cells and basophils without binding or haptenizing to larger carrier molecules.[13] NMBAs are most often implicated in epidemiological studies of anaesthetic drug-induced anaphylaxis.[14–17] Fisher evaluated 134 consecutive patients after anaphylactoid reactions. Using intradermal, passive transfer or subsequent exposure criteria, 67 patients (50%) had reactions to NMBAs.[16] Of the 67 patients reacting to the NMBAs, 54 were women, and the incidence of allergy, atopy and asthma was significantly greater in these patients than in non-reacting patients.[15] Epidemiological data from France suggest that NMBAs are responsible for 62–81% of reactions, depending on the time period evaluated.[2 17–18] The Centre for Allergy and Anaesthesia in Nancy, France, has detected approximately 40 anaphylactic reactions to NMBAs each year since 1982.[2 17–18] Succinylcholine was previously the NMBA most reported; however, in 1996, atracurium and vecuronium had similar incidences to succinylcholine.[18] Reactions to neuromuscular blocking drugs occur more commonly in women.[19]

We have reported previously that aminosteroidal compounds in addition to benzylisoquinoline-derived agents produce positive weal and flare responses when injected intradermally.[3] Our present study defined the clinical concentration for injecting aminosteroidal NMBAs for intradermal testing. Estimates of anaphylactic/anaphylactoid reactions in anaesthesia vary,[11] but we believe that false-positive skin tests overestimate the incidence of rocuronium-induced anaphylactic reactions. We evaluated the clinical database on potential anaphylaxis to rocuronium in the USA and noted that reactions were rare, occurring in approximately 1 in 500 000 doses (unpublished data from Organon Inc., West Orange, NJ). The differences noted in the incidence of reactions may reflect the potential for false-positive weal and flare responses.

NMBAs can also produce direct vasodilation by multiple mechanisms, which include calcium channel block.[6] The false-positive skin tests that were reported to be biopsy-negative for mast cell degranulation clearly confound the interpretation of skin tests in patients who have had life-threatening cardiopulmonary collapse. Dilute solutions of NMBAs need to be used when skin testing for potential allergic reactions to these agents. However, the exact concentration that should be used is unclear. Since skin-testing procedures are important in evaluating potential drug allergies, the threshold for direct vasodilating and false-positive effects must be determined whenever subjects are skin-tested for a particular drug.

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Pharmacokinetics and dynamics of atracurium infusions after paediatric orthotopic liver transplantation†

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We examined the pharmacokinetics and pharmacodynamics of atracurium besylate and its metabolites in children after orthotopic liver transplantation (OLT), as a suitable model for critically ill children. Ten children were studied after OLT on return to the intensive care unit (ICU). The mean (range) age was 36 (7–78) months, and weight 6–24.2 kg. Atracurium was started at induction of anaesthesia and adjusted in the ICU according to clinical need. Neuromuscular block was measured using accelerometry (TOFguard) and the train-of-four (TOF) ratio or count. Arterial plasma samples for atracurium and metabolites taken before, 12-hourly during, and at frequent intervals after the infusion were analysed by HPLC. The mean (range) maximum infusion rate during steady-state conditions was 1.44 (0.48–3.13) mg kg^{-1} h^{-1} and the duration of infusion 36.9 (22.5–98.4) h. Tachyphylaxis was not observed. The mean terminal half-life ($t_{1/2}$) for atracurium was 18.8 (12–32.3) min. The steady-state plasma clearance (CL_{ss}) was 13.9 (7.9–20.3) ml min^{-1} kg^{-1} and the terminal volume of distribution (V_Z) 390 (124–551) ml kg^{-1}; both were higher than in adults after successful OLT. The maximum concentration (C_{max}) of laudanosine was 1190 (400–1890) ng ml^{-1} and $t_{1/2}$ was 3.9 (1.1–6.7) h. The renal clearance of laudanosine was 0.9 (0.1–2.5) ml min^{-1} kg^{-1} and increased with urine flow, but there was no significant relationship with serum creatinine. EEG spikes were confirmed in one child only; the corresponding laudanosine C_{max} was 720 ng ml^{-1}. Monoquaternary alcohol C_{max} was 986 (330–1770) ng ml^{-1} and $t_{1/2}$ 42.9 (30–57.7) min. Mean recovery time on stopping the atracurium infusion to a TOF ratio >0.75 was 23.6 (12–27) min. Atracurium is an effective and safe neuromuscular blocking agent in this population. Laudanosine concentrations are not excessive if graft function is satisfactory.

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It is routine practice to sedate and mechanically ventilate children after orthotopic liver transplantation (OLT) until they are physiologically stable and there is evidence of satisfactory graft function. This ensures adequate oxygenation, and allows the administration of potent analgesic drugs without compromising respiratory function. It is often difficult to control ventilation without the use of a neuromuscular blocking drug. However, as both hepatic and renal dysfunction may occur after OLT, the ideal neuromuscular blocking drug for these patients would be one whose clearance and elimination were independent of these two organs, with inactive non-cumulative metabolites, no effects outside the neuromuscular junction, a relatively short duration of action avoiding the problems of prolonged block, and modest cost. Such an agent does not exist but, of those currently available, atracurium appears to satisfy most of these criteria.

The use of atracurium administered by infusion has been reported in paediatric anaesthesia[1 2] and intensive care,[3 4] but there is little information about its pharmacokinetics and safety in critically ill children at risk of organ system dysfunction. Atracurium is metabolized by a combination of spontaneous degradation in plasma (Hofmann elimination) and ester hydrolysis by plasma esterases. These processes are independent of hepatic and renal dysfunction, and

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atracurium clearance remains relatively uniform and predictable even in adults with fulminant hepatic failure awaiting liver transplantation.[5] However, this is not true of the main breakdown product of Hofmann degradation, laudanosine, which accumulates in these patients until successful graft function has been established.[5] Laudanosine accumulation also occurs in patients with acute renal failure.[6] The importance of this in clinical practice is unknown, but in animals laudanosine can cause electrophysiological seizure activity. The relationship between plasma laudanosine and seizure activity appears to be species-dependent. A steady-state laudanosine concentration of 17 μg ml^{-1} produces seizures in dogs.[7] In cats no EEG evidence of epileptiform activity occurs[8] at plasma laudanosine concentrations of up to 100 μg ml^{-1}. In rabbits, a laudanosine concentration of 5 μg ml^{-1} resulted in purposeless, uncoordinated movements of the entire body.[9] There is one report of concentrations of 19 μg ml^{-1} in a child after inadvertent overdose without any untoward effect.[10] Plasma laudanosine concentrations have been monitored in adult ICU patients receiving atracurium by infusion[11] and in children after a single bolus during surgery.[12] There have been no reports of clinically apparent cerebral effects attributable to laudanosine in humans. The situation in paediatric ICU practice is less clear because of the paucity of information about the fate and potential toxicity of atracurium metabolites in children. The aim of this study was to evaluate the pharmacokinetics and also the efficacy and safety of atracurium infusions in children after OLT.

Patients and methods

After local ethics committee approval, written informed consent for the study was obtained from the parents of 10 children who were to undergo OLT. The mean age (range) was 36 months (7–78). Five were male. The cause of liver failure was biliary atresia with portal hypertension in seven patients; the others had Crigler–Najjar syndrome (congenital deficiency of glucuronyl transferase causing non-haemolytic jaundice), type 1 tyrosinaemia, and hepatitis A (Table 1).

Atracurium was started in the operating theatre with an intravenous bolus of 0.5 mg kg^{-1} followed by an infusion at an initial rate of 0.25 mg kg^{-1} h^{-1}. The infusion was continued throughout the transplantation. On return to the ICU after OLT, the total dose of atracurium used during the procedure was recorded and arterial blood and urine samples were taken for subsequent analysis (see below). Analgesic sedation was provided using a continuous infusion of alfentanil (maximum 1 μg kg^{-1} min^{-1}) supplemented with chloral hydrate 30–50 mg kg^{-1} (maximum 1 g) enterally if required. Neuromuscular block was measured using a peripheral transcutaneous nerve stimulator and an accelerometer. Central and peripheral temperatures were recorded with each plasma and urine sample. The train-of-four (TOF) ratio or TOF count was recorded as appropriate. The atracurium infusion rate was adjusted according to clinical need by the attending ICU medical staff; if there was no spontaneous muscle movement the infusion rate was reduced until a TOF count of more than 1 was recorded. The TOF count or ratio was checked every 30 min for the first 4 h on the ICU and then every 12 h throughout the infusion. The clinical adequacy of muscle relaxation was also noted during the infusion period. When the infusion was stopped, the time taken for clinical recovery and the time for the TOF ratio to reach 0.75 were recorded.

Arterial plasma samples for atracurium and its metabolites were taken from the indwelling arterial cannula on entry to the ICU and every 12 h during infusions. When the infusion was to be discontinued, samples were taken immediately before, then at 5, 10, 20, 30, 60 min and at 2, 6, 12, 24 and 48 h. Each heparinized 2 ml blood sample was centrifuged at 8000 *g* for 60 s, the plasma separated, 0.5 ml was acidified by addition to 2 ml of 15 mM sulphuric acid, mixed by inversion five times, and stored at –20°C. This process was completed within 3 min. Hourly urine volumes were recorded and the urine samples (0.5 ml) were stabilized by addition of 2 ml of cooled 0.5 M citrate buffer and then processed in the same way as the plasma samples.

Table 1 Individual patient diagnoses, biochemical data, PRISM score, laudanosine kinetics, EEG, atracurium infusion data, TOF recovery and outcome
*Aspartate transaminase at end of infusion period (IU/litre); †serum creatinine at end of infusion

Patient	Diagnosis	AST* (IU $litre^{-1}$)	Creatinine† (μmol l^{-1})	PRISM score	Laudanosine C_{max} (ng ml^{-1})	Laudanosine $t_{\frac{1}{2}}$ (h)	EEG spikes	Total dose (mg kg^{-1})	TOF >0.75	Total duration of infusion (h)	ICU outcome
1	Biliary atresia	1770	43	22	1250	4.3	No	22.2	16	22.5	Survived
2	Biliary atresia	1244	27	23	1750	6.1	No	29.1	27	27.4	Survived
3	Crigler–Najjar type 1	1765	61	2	450	–	No	13.0	12	25.8	Survived
4	Biliary atresia	807	42	16	720	3.2	Yes	23.7	21	29.4	Survived
5	Biliary atresia	1050	46	16	400	1.1	No	21.9	14	27.7	Survived
6	Biliary atresia	n/a	n/a	35	–	–	–	4.5	–	11.8	Died
7	Biliary atresia	207	31	16	1330	–	No	35.2	27	48.9	Survived
8	Biliary atresia	57	31	19	1590	–	No	73.9	17	98.4	Survived
9	Tyrosinaemia	181	113	17	1890	6.7	No	30.6	5.2	27.8	Survived
10	Hepatitis A	3800	40	13	1330	1.8	No	27.9	27	23.8	Survived

Samples were analysed at the Department of Bioanalysis and Drug Metabolism, Wellcome Research Laboratories, Beckenham, Kent, UK, using a modified high-performance liquid chromatography (HPLC) technique.[13]

The chromatographic conditions allowed separation and individual measurements of the three geometrical isomers of atracurium. The limit of quantification (LOQ) in plasma was about 5 ng ml^{-1} for the atracurium isomers and assay reproducibility (from the lowest quality control sample at 10 ng ml^{-1}) was 18% (coefficient of variation). The plasma LOQ for the metabolites laudanosine, monoquaternary alcohol (MQA, *cis* isomer) and tetrahydropapaverine (THP) were 100, 70 and 100 ng ml^{-1} respectively, and assay reproducibility at these limits was 12, 14 and 15% respectively.

The non-compartmental pharmacokinetics of atracurium (treated as the sum of the individual isomers), laudanosine, tetrahydropapaverine and the monoquaternary alcohol metabolite was studied. Safety was assessed by monitoring the plasma concentrations of laudanosine and other metabolites, recording adverse events, and daily electroencephalography (EEG). We recorded all drugs prescribed, daily fluid balance and physiological data relating to cardiac, renal, hepatic and cerebral function, and the PRISM (paediatric risk of mortality) score,[14] an index of physiological stability and severity of illness.

Data are presented as either mean (range) or mean (SD). Linear correlation was used to examine univariate relationships; statistical significance was assumed at $P<0.05$.

The following pharmacokinetic abbreviations and calculations are used:

λ_Z = terminal rate constant calculated from the post-infusion concentrations using the Solver function of Excel to minimize the weighted sum of squares function S, where $S = \sum (C-C_{calc}/C)^2$, C is the measured concentration and C_{calc} the calculated concentration given by $C_{calc} = Ae^{-\lambda_Z t}$

$t_{1/2}$ = terminal half-life, $\ln 2/\lambda_Z$

AUC = linear trapezoidal area under the plasma concentration *vs* time curve from time of entry into the ICU to infinity; this was corrected for initial plasma concentrations from operating theatre doses using the first measured concentration C_0 and the terminal rate constant by subtracting (C_0/λ_Z)

$R_{AUC(m)}$ = ratio of metabolite AUC to atracurium AUC; this represents the relative plasma exposure of metabolite to parent compound for the doses given in the ICU (as unknown losses were occurring during surgery)

C_{SS} = steady-state atracurium plasma concentration (considered to be steady state when at least an hour had elapsed without a change in infusion rate or a bolus injection)

C_{max} = maximum concentration

t_{max} = time to maximum concentration

CL_{SS} = steady-state plasma clearance (ml kg^{-1} min^{-1}) = (Infusion Rate/C_{ss})

CL = total plasma clearance = (Total ICU Atracurium Dose/AUC)

V_Z = terminal volume of distribution = (CL/λ_Z)

CL_R = point renal clearance, calculated from a urine concentration C_{urine}, the urinary flow rate Q_{urine} measured over the previous hour, and either the closest or, if infusion rates had not changed, the interpolated, plasma concentration C using $CL_R = Q_{urine}\,(C_{urine}/C)$

Results

Data from nine patients (four male, five female), with successful liver transplants, of age 7–78 months and weight 6.0–24.2 kg, were analysed. The remaining patient (male, age 59 months, weight 15 kg) died shortly after an unsuccessful transplant. In this patient, only C_{max} and t_{max} are reported, because samples after the termination of the atracurium infusion could not be obtained. One patient (patient 9) had chronic renal impairment; the remaining eight patients had normal renal function, as assessed by urine output and serum creatinine concentration (Table 1).

A typical plasma profile together with dosing details on return from the operating theatre is shown in Fig. 1.

A summary of atracurium dose, duration and kinetics is shown in Table 2. The total dose of atracurium ranged from 13 to 73.9 mg kg^{-1} and the period of infusion from 22.5 to 98.4 h. Maximum supplementary bolus doses were 0.48–2.5 mg kg^{-1} (mean 1.28 mg kg^{-1}) and maximum infusion rates were 0.48–3.13 mg kg^{-1} h^{-1} (mean 1.44 mg kg^{-1} h^{-1}). Peak plasma concentrations of atracurium ranged from 887 to 2907 ng ml^{-1} with a mean of 1712 ng ml^{-1}. Patient 10 was excluded from this calculation when C_{max} occurred close to a bolus injection of atracurium immediately after transplantation. Mean $t_{1/2}$ was 18.8 (6.4) min (12.0–32.3 min). Mean V_Z was 390 (152) ml kg^{-1} (124–551 ml kg^{-1}). Mean CL_{SS} was 13.9 (4.2) ml min^{-1} kg^{-1}, similar to the mean CL of 14.7 (5.9) ml min^{-1} kg^{-1}. There were no obvious trends in CL_{SS} with respect to time or infusion rate. The CL_R increased with urine flow rate, averaging 1.7 (1.2) ml min^{-1} kg^{-1} (0.1–3.7 ml min^{-1} kg^{-1}), which was around 12% of the total atracurium clearance.

Peak concentrations of laudanosine ranged from 400 to 1890 ng ml^{-1}, and mean C_{max} was 1190 (548) ng ml^{-1} (Table 3). The mean t_{max} of 29.3 (12.7) h was about 2 h longer than the atracurium t_{max} Half-lives ranged from 1.1 to 6.7 h and the mean laudanosine $t_{1/2}$ was 3.9 (2.3) h. The mean ratio of laudanosine AUC to atracurium AUC ($R_{AUC(m)}$) was 0.98 (0.6) (range 0.3–2.05). Mean CL_R was 0.9 (0.8) ml min^{-1} kg^{-1} (0.1–2.5 ml min^{-1} kg^{-1}). There was no relationship between laudanosine CL_R and plasma creatinine concentration.

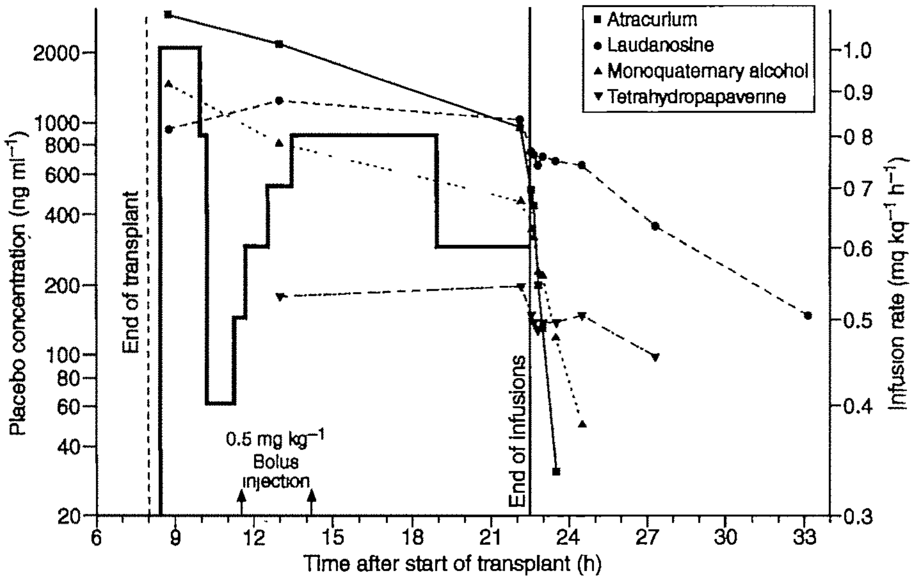

Fig 1 Plasma concentrations of atracurium, laudanosine, monoquatemary alcohol and tetrahydropapaverine for a typical patient. The solid line (right ordinate) shows the infusion rate; arrows indicate bolus doses of 0.5mg kg^{-1}. The vertical dashed line represents the end of transplantation and the vertical solid line the end of infusions, after which terminal half-lives were determined.

Table 2 Atracurium infusion data and kinetics. *Patient 6 excluded; †patient 10 excluded (see text)

	Mean (range)*
Total dose (mg kg^{-1})	30.8 (13.0–73.9)
Duration (h)	36.9 (22.5–98.4)
Max infusion rate (mg kg^{-1} h^{-1})	1.44 (0.48–3.13)
C_{max} (ng ml^{-1})	1712 (887–2907)†
$t_{\frac{1}{2}}$ (min)	18.8 (12.0–32.3)
V_Z (ml kg^{-1})	390 (124–551)
CL_{SS} (ml min^{-1} kg^{-1})	13.9 (7.9–20.3)
CL_R (ml min^{-1} kg^{-1})	1.7 (0.1–3.7)

Table 3 Laudanosine kinetics (n=9) *n=6

	Mean (range)
C_{max} (ng ml^{-1})	1190 (400–1890)
$t_{\frac{1}{2}}$ (h)	3.9 (1.1–6.7)*
Laudanosine:atracurium AUC ratio	1.0 (0.3–2.1)
CL_R (ml min^{-1} kg^{-1})	0.9 (0.1–2.5)

Data for MQA and THP kinetics are shown in Table 4. Renal clearance of all atracurium metabolites increased with urine flow rate.

All patients had a satisfactory level of paralysis, as judged clinically or by transcutaneous nerve stimulation using acceleromyography. Despite prolonged infusion, when atracurium was discontinued the neuromuscular recovery time was rapid (mean 23.7 min with TOF >0.75). There was no clinical or electromyographic evidence of prolonged block. Only one patient demonstrated EEG evidence of spike activity; there was no apparent association with plasma laudanosine concentration (Table 1). No other adverse effects were reported during the study.

Table 4 Kinetics of monoquaternary alcohol (MQA) and tetrahydropapaverine (THP)

	Mean (range)	
	MQA (n=9)	THP (n=3)
C_{max} (ng ml^{-1})	986 (330–1770)	170 (150–200)
$t_{\frac{1}{2}}$ (MQA min, THP h)	42.9 (30.0–57.7)	15.2 (8.4–22)
Metabolite:atracurium AUC ratio	0.6 (0.4–0.9)	0.3 (0.1–0.4)
CL_R (ml min^{-1} kg^{-1})	2.2 (0.2–5.1)	1.3 (0.3–2.3)

Discussion

Although atracurium is used for neuromuscular block in children, there is little published data on the pharmacokinetics of atracurium, especially its metabolites in paediatric patients in general, and none for paediatric intensive care. We chose to study children after OLT because transient impairment of liver and renal function is common after this operation, and they may therefore provide a model for multiple organ dysfunction of relevance to paediatric intensive care practice. Moreover, laudanosine is probably metabolized by the liver[5] and cleared both by this organ and by the kidneys.[6]

The half-lives of atracurium were similar to those reported for healthy children[15] and children with stable impaired liver function.[12] However, volumes of distribution and plasma clearances were much higher than in the other studies. A pharmacokinetic single-dose study[12] comparing children with normal hepatic function with those awaiting liver transplantation showed no differences in atracurium pharmacokinetics (terminal $t_{1/2}$ 19.1 and 20.3 min respectively; CL 5.1 and 5.3 ml min^{-1} kg^{-1}; V_Z 139 and 152 ml kg^{-1}). Our patients after OLT had a similar mean $t_{1/2}$ of 18.8

min but a considerably higher CL of 14.7 ml min^{-1} kg^{-1} and a V_Z of 390 ml kg^{-1}. The constancy of $t_{1/2}$ resulting from the predominance of elimination of atracurium from plasma by Hofmann degradation and ester hydrolysis suggests that the increase in V_Z is a real volume change in paediatric ICU patients. The increase in CL compared with surgical paediatric patients is a consequence of the increase in V_Z and lack of change in $t_{1/2}$. Renal clearance is similar to that reported for adults.[16]

Comparison of these results with those which we have previously reported[5] from adult patients with fulminant hepatic failure (FHF) undergoing liver transplantation shows that adults with functioning grafts have a similar $t_{1/2}$ (17.6 min) but a lower CL (8.5 ml min^{-1} kg^{-1}) and lower V_Z (214 ml kg^{-1}). These comparisons imply that, on a body weight basis, ICU paediatric patients have a larger volume of distribution than corresponding adults, as reported by others.[12 15] This is supported by the relatively lower atracurium infusion C_{max} in our paediatric patients relative to the adult study (1712 *vs* 2723 ng ml^{-1}), even though maximum infusion rates were higher in the children (1.44 *vs* 0.96 mg kg^{-1} h^{-1}). In agreement with the study in children of different ages,[12] the increases in clearance and volume with weight (age) are not so marked if calculated on the basis of body surface area.

Laudanosine C_{max} in the paediatric patients was lower than that in successfully transplanted adults with FHF (1190 *vs* 3993 ng ml^{-1}), probably because of better graft and renal function in the children. Laudanosine $t_{1/2}$ was shorter in children compared with adults (3.9 *vs* 5.3 h) and the laudanosine:atracurium AUC ratio was correspondingly lower at 1.0 *vs* 1.3 in adults, confirming that the higher atracurium CL in children does not lead to greater relative exposure to laudanosine. Renal clearance of all atracurium metabolites increased with higher urine flow rates, a finding which was also reported in our corresponding adult study.[5]

The MQA C_{max} in paediatric patients (986 ng ml^{-1}) was also lower than in adults with fulminant hepatic failure (1457 ng ml^{-1}), $t_{1/2}$ was slightly longer (42.9 *vs* 36.8 min) and the MQA:atracurium AUC ratio was lower (0.6 *vs* 0.8). The pharmacokinetics of THP was only available for three patients, the others having plasma concentrations below the limit of quantification of 100 ng ml^{-1}. The behaviour of THP was broadly similar to that of the other metabolites. C_{max} was lower than that in the adults (170 *vs* 777 ng ml^{-1}) and $t_{1/2}$ shorter (15 *vs* 69 h).

We found the accelerometer an acceptable instrument for monitoring the intensity of, and recovery from, neuromuscular block in these children. An ICU study of accelerometry in neonates and children receiving vecuronium also found the technique useful, and demonstrated lower dose requirements for this neuromuscular blocking drug in those aged less than 1 yr.[17]

In conclusion, we have found that, although children require higher atracurium infusion rates on a body weight basis than adults to produce acceptable degrees of neuromuscular block for assisted ventilation after successful liver transplantation, plasma concentrations of atracurium are lower, because of higher clearance and greater volume of distribution per unit of body weight. Metabolite exposures, judged by ratios of plasma AUCs to those of atracurium, are also lower. These pharmacokinetic properties of atracurium make it a suitable choice for further evaluation in paediatric intensive care practice.

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Simultaneous determination of neuromuscular block at the larynx, diaphragm, adductor pollicis, orbicularis oculi and corrugator supercilii muscles

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We simultaneously determined the neuromuscular blocking effect of mivacurium 0.2 mg kg^{-1} at five muscles in 20 women undergoing gynaecological surgery. Evoked electromyographic responses were obtained using surface electromyography (EMG) at the adducting laryngeal muscles, the diaphragm (lateral to vertebrae T12/L1 or L1/L2) and the adductor pollicis muscle and acceleromyographic (AMG) responses were measured at the orbicularis oculi and the corrugator supercilii muscle. Onset time and times for the first twitch response (T_1/T_0) to return to 25, 75 and 90% at the adducting laryngeal muscles and the diaphragm were significantly ($P<0.005$) shorter than at the adductor pollicis, the corrugator supercilii or the orbicularis oculi muscles (mean (SD) onset time: 89 (26) s and 78 (17) s to 202 (45) s, 152 (41) s, 194 (40) s; T_1/T_0=25%: 10.4 (1.5) and 11.4 (1.2) min *versus* 20.5 (3.9), 15.9 (3.3), 16.3 (3.7) min; T_1/T_0=90%: 15.5 (1.6) and 16.1 (1.6) min *versus* 27.4 (4.6), 21.5 (3.8), 23.3 (5.1) min). Onset and clinical duration of neuromuscular block at the larynx and the diaphragm after mivacurium 0.2 mg kg^{-1} are shorter than in the peripheral muscles. Monitoring of neuromuscular block in the diaphragm was successfully used in all patients.

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In recent years, attempts have been made to measure onset and offset of neuromuscular block at various muscles The monitoring of the response of the larynx and the diaphragm to neuromuscular blocking drugs has enhanced our knowledge about the action of these agents and delivered more accurate data on the onset and clinical duration of neuromuscular block at those muscles. The determination of neuromuscular block by the introduction of a cuff-pressure technique for measurements at the larynx[1] and electromyographic (EMG) monitoring of the diaphragm[2] have replaced simple clinical observation in the study of neuromuscular block.[3] The great inter-individual range of the pharmacodynamic profile of non-depolarizing neuromuscular blocking drugs makes the intra-individual comparison of onset and offset interesting.

We simultaneously determined the onset and offset of neuromuscular block produced by mivacurium 0.2 mg kg^{-1} at the larynx, diaphragm, adductor pollicis, orbicularis oculi and corrugator supercilii muscle using non-invasive, superficial electrodes. To record the diaphragmatic response, we modified the technique of skin EMG by placing the electrodes at the back of the patient, lateral to vertebrae T12/L1 or L1/L2, just inferior to the 12th rib, thus presenting a novel site for monitoring diaphragmatic neuromuscular block.

Materials and methods

After approval of the local ethics committee and written informed consent, 20 women undergoing gynaecological surgery were included in the study. Pregnant women, patients with neuromuscular, hepatic or renal disease and patients receiving medications known to interact with neuromuscular blocking drugs were excluded.

Anaesthesia was induced using alfentanil 20 μg kg^{-1} followed by a target-controlled infusion of propofol (target concentration 4 μg ml^{-1}) programmed to reach the target concentration within 30 s. After induction of anaesthesia, the trachea was intubated through the mouth using a Woodbridge tube (Mallinckrodt, UK, size 7.0) with the surface laryngeal electrode (Magstim company, UK) attached 2 cm above the origin of the cuff. The electrode

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was placed between the vocal cords for optimal EMG tracing.[4] Anaesthesia was maintained with a target-controlled infusion of propofol (target concentration 3 μg ml^{-1}) and alfentanil in increments of 10 μg kg^{-1} given at the discretion of the anaesthetist; mechanical ventilation was adjusted to achieve an end-tidal carbon dioxide-pressure of 3.5–4.5 kPa.

Two Ag/AgCl-skin-electrodes were attached lateral to vertebrae T12/L1 or L1/L2 (wherever the maximum response was better) on the right paravertebral side of the back, inferior to the 12th rib, and placed 2 cm apart for monitoring of the response of the right diaphragmatic muscular crux to phrenic nerve stimulation[5] (Fig. 1). One Ag/AgCl-electrode was used as a ground electrode and placed on the hip bone distant to the recording site.

The phrenic and recurrent laryngeal nerves were stimulated transcutaneously using one external bipolar nerve stimulator (Multiliner®, Tönnies company, Germany) on the right side at the inferolateral edge of the sternocleidomastoid muscle for the phrenic nerve. In addition, two Ag/AgCl electrodes were positioned over the notch of the thyroid cartilage on the same side for the recurrent laryngeal nerve.[1] The stimulation site was selected, which produced only minimal or no concomitant stimulation of the brachial plexus. The probe of the external nerve stimulator is attached at the neck with an elastic band. It delivers a current between 0 and 70 mA. Single twitch-stimulation (0.1 Hz, pulse width 0.2 ms) was performed on the right neck to determine the supramaximal stimulation and recorded using modified Multiliner® (Toennies, Germany) nerve conduction software. The current was increased from 0 mA to the current with the maximal EMG response and then increased by 10 mA to assure supramaximal stimulation. The amplitudes of the diaphragmatic and the laryngeal compound action potentials (peak-to-peak) were measured and recorded (Fig. 2). After stimulation of the right ulnar nerve using Ag/AgCl-electrodes attached to the forearm, evoked EMG-single twitch responses (0.1 Hz; pulse width 0.2 ms) from the adductor pollicis muscle via Ag/AgCl-electrodes placed over the base of the thenar area were recorded. The automatic calibration of the Datex Relaxograph® NMT 100 (Datex Instrumentarium Corporation, Helsinki, Finland) was used to determine supramaximal stimulation (0–70 mA).

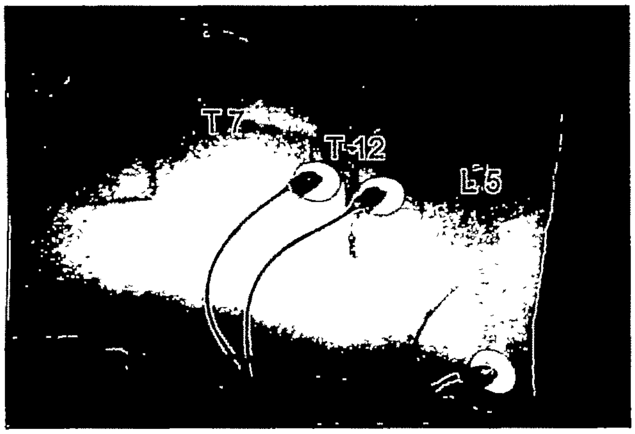

Fig 1 Position of the recording electrodes; marked are T 7, T 12, 12th rib; electrodes are placed 2 cm apart at T 12/L1 or L1/L2, wherever the response is better (the third electrode is the ground electrode).

An AMG probe was placed on the medial part of the right superciliary arch was equipped with an AMG probe (TOF$^{\text{NMT}}$-guard, eye-adapter, Organon Teknika, Finland) to record the neuromuscular response of the corrugator supercilii muscle. Another AMG probe was placed on the left upper eye lid to record evoked responses of the orbicularis oculi muscle [6] Stimulation of the upper branches of the facial nerves was performed on both sides using two Ag/AgCl-electrodes (size 1×1.5 cm) attached to the skin 2 cm anterior to the ear lobe. The automatic calibration set-up of the TOF-guard$^{\text{INMT}}$ (Organon Helsinki, Finland) was used to determine supramaximal stimulation on both sides (single twitch, 0.1 Hz). After no change in the neuromuscular response could be detected at all five sites for 10 min,

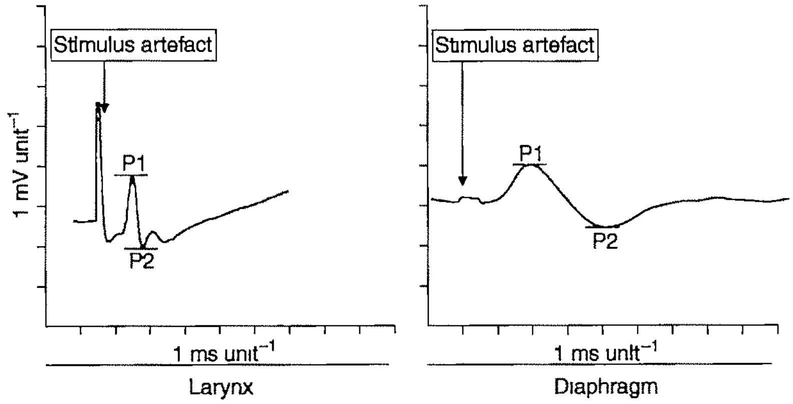

Fig 2 Compound action potential of the electromyographic response of the laryngeal muscles and the diaphragm for a representative patient, amplitude P1–P2 measured as muscular response (lines mark measurement points).

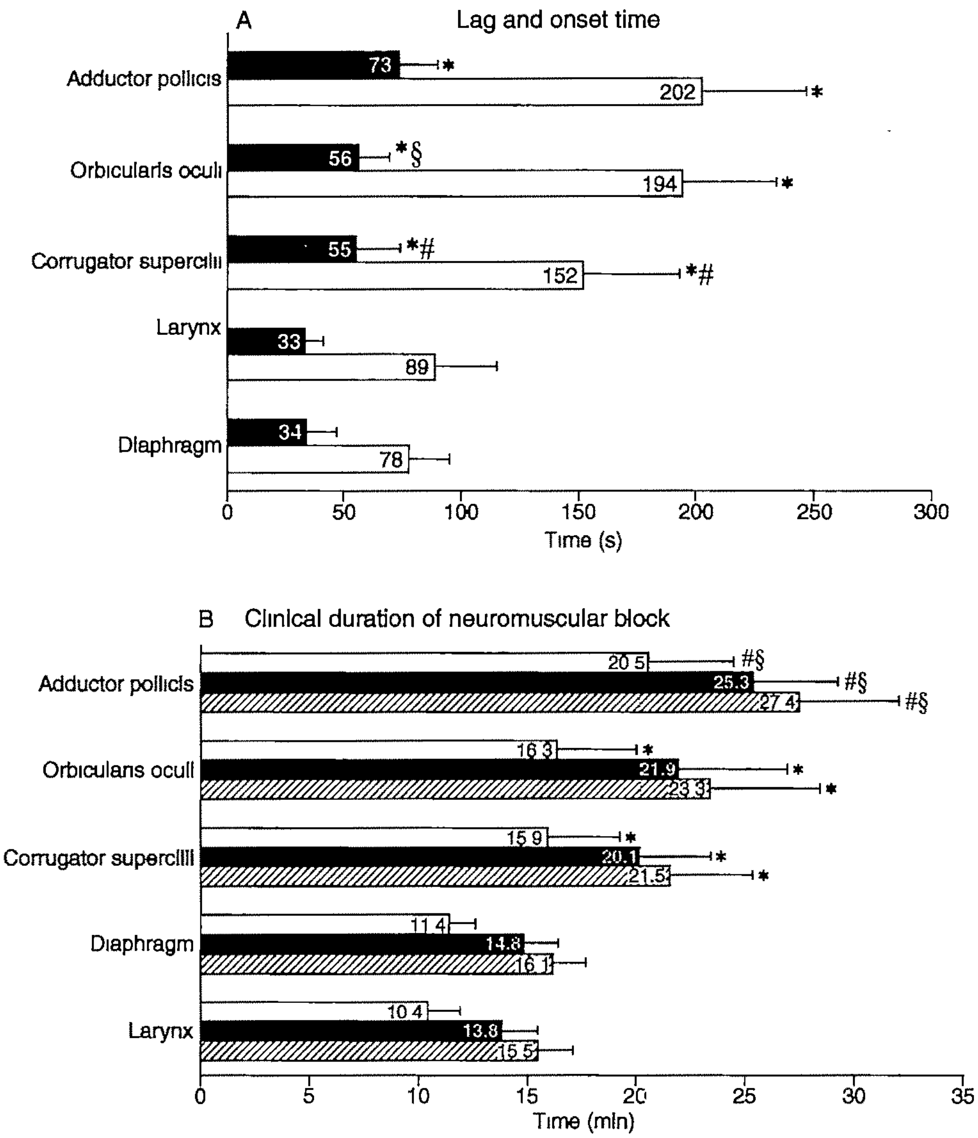

Fig 3 Onset and clinical duration of neuromuscular block after mivacurium 0.2 mg kg^{-1} Values are mean, error bars indicate standard deviation The larynx, the diaphragm and the adductor pollicis muscle monitored using EMG, the orbicularis oculi and the corrugator supercilii muscle are measured using AMG. (A) Lag time (black column) and onset time (white column): time from injection of mivacurium to the first and maximal effect; $*P<0.005$ *versus* larynx and diaphragm, $\#P<0.025$, $\S P<0.005$ *versus* adductor pollicis muscle, respectively. Mean time in box. (B) $T_1/T_0=25\%$ (white column), $T_1/T_0=75\%$ (black column), $T_1/T_0=90\%$ (striped column): time from injection to recovery of the twitch response to 25, 75 and 90% $*P<0.05$ *versus* larynx and diaphragm, $\#P<0.005$ *versus* larynx and diaphragm, $\S P<0.05$ *versus* corrugator supercilii muscle.

the patients received mivacurium 0.2 mg kg^{-1}, injected within 15 s into a fast-flowing infusion of Ringer solution. No further dose of neuromuscular blocking drug was given. Body temperature was measured at the forehead and kept above 35.6°C using a heating blanket (Bair Hugger, MN, USA).

The time from the end of injection of mivacurium to the first twitch depression (lag time), the maximum twitch depression (onset time) and the maximum block (%-reduction of the maximal neuromuscular response) were measured. To determine clinical duration of neuromuscular block, single-twitch responses every 15 s were used; time for the first twitch response (T_1/T_0) to return to 25, 75 and 90% was measured.

Statistical analysis

The results are expressed as mean (standard deviation (SD)) and range. The pharmacodynamic parameters were compared between the different monitoring sites using analysis of variance (ANOVA), followed by Fisher's least significant difference strategy for multiple comparisons; $P<0.05$ was regarded as showing a significant difference.

Results

In 20 female patients with a mean age of 44 (SD 16) yr (range 18–78 yr) and a mean weight of 64 (10) kg (46–81 kg), determination of the supramaximal stimulation at all five monitoring sites was successful. No side effects as a result of the simultaneous transcutaneous stimulation of the recurrent laryngeal and phrenic nerve with a mean current of 45 (6) mA (range 30–55 mA) such as arrhythmias or skin irritation were noted.

Mean maximum block was more than 98% at all sites. It was 99 (SD 4)% (range 88–100%) and 99 (4)% (range 82–100%) at the larynx and the diaphragm, respectively. The mean maximum block at the adductor pollicis, the corrugator supercilii and the orbicularis oculi muscle was 99 (2)% (93–100%), 99 (3)% (84–100%) and 98 (4)% (86–100%), respectively. There was no statistically significant difference between the muscles.

Onset times and clinical duration of neuromuscular block are presented in Figure 3A and Figure 3B. Lag time and onset time of neuromuscular block were significantly shorter at the larynx and the diaphragm than at the other muscles ($P<0.005$), without being significantly different between the diaphragm and the larynx or between the orbicularis oculi and the corrugator supercilii muscle.

The lag and onset time at the adductor pollicis muscle were significantly longer than the times at the corrugator supercilii muscle ($P<0.025$); although the lag time at the adductor pollicis muscle was significantly longer than the lag time at the orbicularis oculi muscle ($P<0.005$), the onset times at the adductor pollicis and the orbicularis oculi muscle did not differ statistically (202 *versus* 194 s). Time for the first twitch response (T_1/T_0) to return to 25, 75 and 90% was shorter for the larynx and the diaphragm than for the other muscles ($P<0.05$ *versus* the orbicularis oculi and the corrugator supercilii muscle, $P<0.005$ *versus* the adductor pollicis muscle).

The clinical duration of neuromuscular block at the corrugator supercilii muscle was significantly shorter than at the adductor pollicis muscle ($P<0.05$), but not statistically different from the clinical duration at the orbicularis oculi muscle.

Discussion

The simultaneous determination of neuromuscular block after mivacurium 0.2 mg kg^{-1} at the larynx, diaphragm, adductor pollicis, orbicularis oculi and corrugator supercilii muscle revealed that onset at the respiratory muscles (larynx, diaphragm) reaches a mean maximum block of 99% after 80–90 s, whereas the onset at the orbicularis oculi and the corrugator supercilii muscle is more than 150 s and at the adductor pollicis muscle is more than 3 min. Time for T_1/T_0 to reach 25% was 10–12 min at the larynx and the diaphragm, more than 15 min at the orbicularis oculi and corrugator supercilii muscle and more than 20 min at the adductor pollicis muscle.

The onset times determined in this study correspond well with times determined by judging the intubating conditions at the larynx and the diaphragm, but the responses are in contrast to visual observation of the orbicularis oculi response to stimulation.

Le Corre and colleagues[7] estimated the onset of several neuromuscular blocking drugs at the orbicularis oculi muscle and found that visual estimation was a good predictor of excellent or good intubation conditions. They concluded that loss of orbicularis oculi responses are acceptable predictors of good intubation conditions. They estimated an onset time of 99 s at the orbicularis oculi muscle after mivacurium 0.2 mg kg^{-1} and performed tracheal intubation with good to excellent intubation conditions. This would be in concordance with the diaphragmatic and laryngeal onset times measured in this study (78 and 89 s) but not with another study which compared the effects of mivacurium 0.2 mg kg^{-1} at the diaphragm and the geniohyoid muscles. D'Honneur and colleagues[8] determined the onset time at the diaphragm, using surface EMG at 158 s longer than it was in our study. The major difference between their study and this one is the different calibration time: whereas D'Honneur and colleagues only waited 3 min before measurements were started, the current study set-up used a 10-min calibration time of supramaximal stimulation. McCoy and colleagues[9] found that the longer the duration of control stimulation the shorter the onset measured.

Rimaniol and colleagues[6] studied the effect of mivacurium 0.15 and 0.25 mg kg^{-1} at the orbicularis oculi muscle using AMG. They found that for mivacurium 0.15 mg kg^{-1} the onset of neuromuscular block was not different between the orbicularis oculi and the adductor pollicis muscle (235 (SD 76) *versus* 232 (67) s), but the offset was significantly shorter at the orbicularis oculi muscle. For mivacurium 0.25 mg kg^{-1}, the onset was significantly shorter at the orbicularis oculi muscle than at the adductor pollicis muscle (90 (25) *versus* 160 (30) s). In the current study, the onset of block after mivacurium 0.2 mg kg^{-1} was shorter at the orbicularis oculi muscle than at the adductor pollicis muscle (194 (40) *versus* 202 (45) s) but failed to reach statistical significance.

We stimulated the phrenic and the recurrent laryngeal nerve transcutaneously without difficulty. It could be that in patients with large necks or an enlargened thyroid gland, transcutaneous stimulation of the phrenic nerve using a surface probe might be difficult; in those patients, we prefer percutaneous stimulation via needle electrodes. Concomitant stimulation of the brachial plexus was absent or minimal and did not affect the monitoring of the diaphragmatic response; monitoring the diaphragm on the patient's back is certainly advantageous to rule out artefacts from concomitant stimulation of the brachial plexus.

Donati and colleagues[2] introduced surface EMG of the diaphragm to monitor neuromuscular block into research practice; it was an easy and objective way to measure onset and offset of block at this muscle. Skin electrodes attached at the 7th or 8th intercostal space between the mid-clavicular and the anterior axillary line, however, cannot be used during open and laparoscopic abdominal surgery as they are within the surgical fields.

Because the muscular crura of the lumbar diaphragm are inserted into the first two to three lumbar vertebrae, it seemed possible to monitor the response to phrenic stimulation on the patient's back, lateral to vertebrae T12/L1 or L1/L2 (Fig. 2). Future studies will show whether this location can be used for routine intra-operative monitoring of the diaphragm.

The corrugator supercilii muscle, a small muscle of the superciliary arch, located medially under the eyebrow, is inserted into the forehead skin and responsible for vertical frowning of the forehead. It can be monitored using an AMG probe attached to the medial part of the superciliary arch at a 90° angle to the muscle contraction direction, in a similar way to the AMG measurement of the orbicularis oculi muscle.[6 10]

The only study of neuromuscular block at the corrugator supercilii muscle was recently presented as an abstract by Plaud and Donati.[11] They measured maximum block and recovery to $T_1/T_0=25\%$ after rocuronium 0.6 mg kg^{-1} at the corrugator supercilii muscle and the larynx. They concluded that the neuromuscular response measured at the corrugator supercilii muscle was a good reflection of the laryngeal muscle response. We found significant differences in onset time and clinical duration between the larynx and the corrugator supercilii muscle but the maximum block was not significantly different.

The morphological difference between the orbicularis oculi muscle and the corrugator supercilii muscle has been the focus of a recent anatomical study. Goodmurphy and colleagues[12] have found that the orbicularis oculi muscle fibres are small, rounded and 89% fast-twitch type-II-muscle fibres, whereas the corrugator supercilii muscle fibres were larger, polygonal, and 49% of fast-twitch type II. The capillary index (capillary area per unit of contractile area) of the corrugator supercilii muscle, however, was 2.4 times the capillary index of the orbicularis oculi muscle. The difference in capillary index and the larger size of the muscle fibres[13] might explain the faster onset of neuromuscular blocking drugs at the corrugator supercilii muscle. Further studies of the action of other neuromuscular blocking drugs at the corrugator supercilii muscle are needed to define the role of this muscle as a predictor of the laryngeal muscle response.

In conclusion, we present the first simultaneous determination of neuromuscular block at the larynx, diaphragm, adductor pollicis, orbicularis oculi and corrugator supercilii muscle. Surface electrodes were used to record evoked responses at all sites. The monitoring of the diaphragmatic response at the back of the patient allows intra-operative monitoring during abdominal surgery. In contrast to previous findings with rocuronium,[11] onset and clinical duration of neuromuscular block after mivacurium at the corrugator supercilii muscle did not accurately reflect onset and clinical duration of neuromuscular block at the larynx or the diaphragm. More studies are needed to define the role of this muscle for neuromuscular monitoring in clinical practice.

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Pre-operative oral erythromycin reduces residual gastric volume and acidity

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We investigated whether low-dose erythromycin (200 mg) given as an oral premedicant altered the residual gastric volume and its acidity in fasted patients at induction of anaesthesia. In a single-blinded study. Sixty patients were allocated randomly to receive either an erythromycin tablet (200 mg) or nothing with 10 ml water 3 h before induction of anaesthesia, and another 60 patients 1 h before induction of anaesthesia. Oral erythromycin significantly reduced residual gastric volume when it was given approximately 3 h ($P<0.05$; 95% CI for median difference: 0.1–17 ml) or 1 h ($P<0.0005$; 95% CI for median difference: 6–24 ml) before induction of anaesthesia. Erythromycin significantly reduced gastric acidity when it was given 1 h before induction of anaesthesia ($P<0.02$; 95% CI for median pH difference: 0.1–1.7). In contrast, when given 3 h before induction of anaesthesia, erythromycin did not significantly alter acidity.

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Pulmonary aspiration of gastric contents remains one of the major causes of death related to anaesthesia. Although routine use of aspiration prophylaxis is unnecessary, it may be performed in certain groups of patients, such as pregnant women undergoing Caesarean section.[1]

Erythromycin, a macrolide antibiotic, at therapeutic doses (500–1000 mg), induces strong and continuous gastric contractions[2 3] and may often cause gastrointestinal symptoms.[4 5] In contrast, at lower doses (up to about 200 mg), it induces intermittent contractions in the stomach, and the contractions migrate into the intestine.[2 3 6] Several studies have shown that a sub-therapeutic dose of erythromycin accelerates gastric emptying of both solids and liquids in healthy volunteers[7] as well as in patients with delayed gastric emptying due to several pathological reasons.[7 8] Erythromycin also has other gastrointestinal prokinetic effects.[9]

Mechanisms for gastric emptying during the fed and the fasted state differ considerably. Therefore, drugs, which accelerate gastric emptying of ingested food, may not reduce residual gastric juice during the fasted state.[10] There has been only one report regarding the effect of erythromycin on residual gastric volume and its acidity.[11] In that study, a therapeutic dose of erythromycin (500 mg) injected intravenously significantly decreased residual gastric volume and acidity.[11] Erythromycin could be used as a premedicant for prophylaxis of aspiration pneumonitis if erythromycin at a sub-therapeutic dose produces a similar effect by oral administration. It is not known if this regimen is effective, since erythromycin can easily be inactivated by gastric juice.[12] Therefore, we studied if a sub-therapeutic dose of erythromycin 200 mg given as an oral premedicant altered the residual gastric volume and its acidity in fasted patients scheduled for elective surgery.

Patients and methods

We studied two sets of 60 patients (total 120 patients), ASA physical status I or II, undergoing elective surgery, in whom tracheal intubation was indicated. Patients were excluded if they had any pathology of the upper respiratory or upper alimentary tract, were at risk of pulmonary aspiration of gastric contents, or if they were taking drugs which were known to alter gastric motility. Institutional Research Ethics Committee approved the study and written informed consent was obtained from all patients.

The patient was asked not to eat solid food for at least 5 h and not to drink liquids for 3 h before the start of the study. No premedicants were given. In the first set of 60 patients, we studied if oral erythromycin, given approximately 3 h before induction of anaesthesia, reduced gastric volume. In this set of patients we decided to give erythromycin 3 h

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Table 1 Patients' characteristics (mean (SD) [range]) In the first set of patients, either water 10 ml (group W_3) or an erythromycin tablet 200 mg with 10 ml water (group E_3) was given 3 h before induction of anaesthesia. In the second set of patients, either water 10 ml (group W_1) or an erythromycin tablet 200 mg with 10 ml water (group E_1) was given 1 h before induction of anaesthesia

	Group W_1	Group E_1	Group W_3	Group E_3
Age	46 (14) [20–65]	43 (16) [20–68]	50 (12) [24–65]	48 (13) [26–70]
Height	162 (8) [148–176]	166 (8) [150–179]	162 (9) [148–183]	166 (9) [147–183]
Weight	61 (12) [41–95]	61 (10) [45–94]	62 (11) [44–86]	66 (12) [47–96]
Male/female	18/12	20/10	15/15	18/12

Table 2 Residual gastric volume (ml) and its acidity (pH) (median [95% CL]). In the first set of patients, either water 10 ml (group W_3) or an erythromycin tablet 200 mg with 10 ml water (group E_3) was given 3 h before induction of anaesthesia. In the second set of patients, either water 10 ml (group W_1) or an erythromycin tablet 200 mg with 10 ml water (group E_1) was given 1 h before induction of anaesthesia

	Volume (ml)	*P*	Acidity (pH)	*P*
Group W_1 (n=30)	26.5 [15.5, 35.8]	–	1.8 [1.8, 2.0]	–
Group E_1 (n=30)	10.0 [5.2, 14.8]	–	2.8 [2.0, 4.0]	–
Group W_3 (n=30)	27.5 [18.0, 32.0]	–	2.0 [2.0, 2.8]	–
Group E_3 (n=30)	13.0 [7.2, 21.5]	–	2.3 [2.0, 3.5]	–
Differences between groups				
Group E_1–Group W_1	–14 [–24, –6]	<0.0005	0.4 [0.1, 1.7]	< 0.02
Group E_3–Group W_3	–9 [–17, 0]	<0.05	0.1 [0, 1.0]	0.29

preoperatively so that any untoward gastrointestinal symptoms could be identified and treated before induction of anaesthesia. We planned to give erythromycin 1 h before the induction of anaesthesia, if erythromycin significantly reduced residual gastric juice without producing gastrointestinal symptoms in this first set of patients.

Patients were allocated randomly to one of two groups. Block randomization (in blocks of 12) was used for allocation, and cards indicating allocations were placed in serially numbered, sealed opaque envelopes. In one group, an erythromycin stearate tablet 200 mg (Erythrocin, Dainippon Pharmaceuticals, Japan) with 10 ml water were given orally, whereas in the other group, only 10 ml water was given. We did not blind the patients from allocation, since placebo tablets were not available.

Since we found that erythromycin tablet given approximately 3 h before induction of anaesthesia significantly reduced residual gastric juice without producing gastrointestinal symptoms (see Results), we decided to study the effect of erythromycin given approximately 1 h before induction of anaesthesia. The second set of 60 patients were allocated randomly to one of two groups, and 10 ml water with and without a 200 mg erythromycin tablet was given orally approximately 1 h before induction of anaesthesia.

In the operating theatre, anaesthesia was induced with propofol and neuromuscular blockade produced with vecuronium; anaesthesia was maintained with sevoflurane and nitrous oxide in oxygen. After the patient's trachea was intubated, residual gastric contents were collected via a gastric tube[13 14] by a researcher who was blinded. A 18-Fr multi-orificed Salem Sump gastric tube (Argyle, St Louis, Missiouri, USA) was inserted orally and correct placement was confirmed by auscultation of bubbling sounds over the epigastrium during insufflation of air through the catheter. Residual gastric contents were collected using a syringe, and its volume and acidity were measured. Gastric acid was measured using a set of pH test papers (Toyo Roshi Kaisha, Tokyo, Japan) which consist of two-step indicators: one test paper indicated pH with a sensitivity of 1 (1–11) and the second set with a sensitivity of 0.2 for the order of 0.1.

Statistical analysis

The normal plot and Shapiro-Francia W' test showed that the volume and pH of residual gastric contents were not normally distributed. Therefore, the Mann-Whitney *U* test was used to compare the volume or acidity between the two groups in each set of groups. $P<0.05$ was considered significant.

The 95% confidence limits (CL) for medians for the volume and pH in each group were calculated using the SINTERVAL commend (sign test) in Minitab release. CLs for the median differences between groups were also calculated.

From previously reported studies[15] and a preliminary study, the mean residual gastric volume at induction of anaesthesia in fasted patients would be about 25 ml (with standard deviation (SD) of approximately 15). We considered that a 50% reduction (i.e. 12.5 ml) in residual gastric volume would be clinically relevant difference. Sixty patients would be required to detect this difference, with a power of 90% and P=0.05.

Results

The ages, heights, weights and sex ratios of groups were generally similar (Table 1).

Oral erythromycin significantly reduced residual gastric volume when it was given approximately 3 h ($P<0.05$; 95% CI for median difference: 0–17 ml) or 1 h ($P<0.0005$; 95% CI for median difference: 6–24 ml) before induction of anaesthesia (Table 2).

Erythromycin significantly reduced gastric acidity when it was given 1 h before induction of anaesthesia ($P<0.02$; 95% CI for median pH difference: 0.1–1.7). In contrast, when given 3 h before induction of anaesthesia, erythromycin did not significantly alter acidity (Table 2).

No patients complained of abdominal discomfort, nausea or vomiting preoperatively.

Discussion

We found that a sub-therapeutic dose of erythromycin (200 mg) given orally either 1 or 3 h preoperatively significantly reduced residual gastric volume and it also significantly decreased gastric acidity when given 1 h preoperatively.

The mechanism of gastric emptying of ingested food differs markedly from that of emptying of residual gastric contents during the fasting state.[16] During the fed state, the stomach empties its contents by continuous irregular motility, whereas during the fasted state gastric motility is not constant and increases and decreases at a fixed cycle, which is regulated by the interdigestive migrating motor complex.[17] The complex, a typical gastrointestinal activity that occurs during the interdigestive (fasting) state, is a cyclical motor pattern which usually originates in either the stomach or duodenum, and migrates to the terminal ileum.[18] The motor complex consists of three main phases: after a period of quiescence (phase 1), an irregular spiking activity occurs (phase 2), which is taken over by intense bursts of action potentials (phase 3 or activity front).[18] Gastric juice accumulates during phase 1 and 2, but during phase 3 the stomach strongly contracts and empties the residual gastric contents.[17] In man, this strong contraction occurs every 1.5 to 2 h.[19]

Motilin, a 22-amino acid gastrointestinal peptide whose receptors are abundant in the stomach,[20] is likely to be involved in initiating the migrating motor complex.[3 6 20 21] Injection of exogenous motilin induces gastric contractions which migrate to the intestine.[6] In addition, injection of a motilin antiserum disrupts the natural migrating motor complex until plasma motilin concentration returns to the physiological level.[21] Furthermore, during the interdigestive state, plasma motilin concentration fluctuates, and there is a close correlation between the peak plasma motilin concentration and motor complex cycle.[3]

Erythromycin is considered to induce the phase 3 of the migrating motor complex, even during the fed state,[22 23] as a motilin receptor agonist. First, binding studies have confirmed that erythromycin displaces the binding of a radiolabelled motilin.[24] Second, the stimulatory effect of erythromycin is decreased in animals tolerant to motilin.[25] Third, injection of erythromycin increases plasma motilin concentration in dogs.[6] Therefore, it was likely that erythromycin significantly decreased residual gastric contents by inducing phase 3 in our patients.

A sub-therapeutic dose of oral erythromycin decreased gastric acidity in our study. This result is consistent with a previous study of the effect of erythromycin injected intravenously during fasting state[11] or during continuous enteric feeding.[26] The mechanisms for the inhibitory effect of erythromycin is not known. One possibility is that gastric acidity decreased by emptying of gastric juice. However, this is unlikely, since one study showed that residual gastric contents decreased during hunger contractions (without any medication), but gastric acidity increased.[17] More likely possibility is that erythromycin decreased gastric acidity by direct action, possibly through motilin receptors. First, motilin also inhibits gastric acid secretion in animals.[27 28] Second, infusion of acid solution into the stomach inhibits phase 3 of the migrating motor complex and decreases plasma motilin concentration, indicating that there is a relation between plasma motilin concentration and intragastric acidity.[29] Third, erythromycin has a direct action to the stomach, since both erythromycin and motilin stimulate pepsinogen secretion from the chief cell of the isolated guinea-pig stomach.[30]

The H_2 histamine receptor antagonists inhibit secretion of gastric juice and acid, and has no influence on the volume and acidity of gastric juice that is already in the stomach. Therefore, these drugs may not effectively reduce gastric volume and acidity within 60–90 min. In contrast, erythromycin can reduce residual gastric juice by stimulating gastric emptying and, thus, it is possible that residual gastric juice would be reduced shortly after administration of erythromycin. Therefore, we were interested to see if erythromycin could reduce gastric volume and acidity 1 h after oral administration. Time to reach peak plasma concentration after oral administration of an erythromycin tablet has been reported to be 2–3 h (manufacturer's information sheet). Therefore, it can be deduced that erythromycin can reduce gastric volume and acidity at much lower plasma concentration than a therapeutic concentration as an antibiotic.

One major complication of erythromycin is gastrointestinal symptoms. Most subjects experience gastric discomfort, and some of them nausea and vomiting if a therapeutic dose of erythromycin is infused intravenously.[4 5] In contrast, in our study, no patient had such symptoms after oral administration of a sub-therapeutic dose. It has been shown that there is a significant correlation between severity of symptoms and infusion rate or between symptoms and plasma erythromycin concentration.[5]

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Dexamethasone for prophylaxis of nausea and vomiting after epidural morphine for post-Caesarean section analgesia: comparison of droperidol and saline

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We have evaluated the prophylactic effect of i.v. dexamethasone 8 mg in preventing nausea and vomiting during epidural morphine for post-Caesarean section analgesia. Droperidol 1.25 mg and saline served as the control. We studied 120 parturients (n=40 in each group) receiving epidural morphine for post-Caesarean section analgesia, in a randomized, double-blind, placebo-controlled study. All parturients received epidural morphine 3 mg. Both dexamethasone and droperidol significantly decreased the total incidence of nausea and vomiting compared with saline, with incidences of 18, 21 and 51% for the three treatments respectively ($P<0.01$ and $P<0.05$ respectively). Parturients who received droperidol reported a more frequent incidence of restlessness (16%) than those who received dexamethasone ($P<0.05$)

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Epidural morphine has a potent and long-acting analgesic effect on postoperative pain.[1–5] It is very convenient for clinical use and is widely accepted for analgesia after Caesarean section.[5–8] However, high incidences of nausea and vomiting (30–65%) have been reported.[9–11] Among the antiemetics used currently, 5-HT_3 antagonists (e.g. ondansetron, granisetron) possess good efficacy, but cost limits their use.[12–15] Dopamine receptor antagonists (e.g. droperidol, prochorperazine, metoclopramide) are commonly used but are associated with a variety of extrapyramidal symptoms.[16 17] Antihistaminic and anticholinergic drugs (e.g. scopolamine, hydroxyzine, promethazine) are also effective, but excessive sedation and tachycardia may occur.[9 18 19]

Dexamethasone is an effective antiemetic after single-dose administration. [11–15 20–23] It is effective in preventing chemotherapy-related emesis and postoperative nausea and vomiting (PONV).[12–15 20–23] Recently, it has also been found to be effective in preventing nausea and vomiting related to epidural morphine in patients undergoing abdominal hysterectomy.[11] We conducted a randomized, double-blinded and placebo-controlled study to evaluate whether dexamethasone was also effective in preventing nausea and vomiting after epidural morphine for post-Caesarean section analgesia.

Patients and methods

The protocol was approved by the Hospital Committee for Human Investigation and informed consent was obtained from each parturient. One hundred and twenty parturients (ASA I–II; 20–35 yr) scheduled for elective Caesarean section under epidural anaesthesia were enrolled in this randomized, double-blind, placebo-controlled study.

No premedication was given. Surgical analgesia to T_4 dermatome level was provided by a dose of 2% lignocaine 15–18 ml (with 1:100 000 epinephrine), followed by intermittent small-dose injections of 2% lignocaine (with epinephrine) as necessary through an epidural catheter in the L3–4 or L4–5 interspace. Lactated Ringer's solution 500 ml was given i.v. before surgery. After delivery of the baby, 10 units of i.v. oxytocin and 0.2 mg of i.m. ergonovine were given to all parturients. Estimated fluid deficit and maintenance requirements were replaced with lactated Ringer's solution i.v. During surgery, i.v. midazolam 2.5 mg was

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given for sedation after delivery of the baby; no supplementary analgesic was given.

Before surgery, a randomization table was used to assign parturients to one of three groups (*n*=40 for each group). At the end of surgery, the dexamethasone group received i.v. dexamethasone 8 mg (2 ml), the droperidol group received i.v. droperidol 1.25 mg (2 ml) and the saline group received i.v. saline (2 ml). One minute later, all parturients received 3 mg of preservative-free morphine in 10 ml of normal saline through the epidural catheter for postoperative analgesia. The randomization process and the identity of the study drugs were blinded from the parturients, the anaesthetists during surgery and the investigators who collected the postoperative data.

The incidences of nausea and vomiting were recorded for 24 h. Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; vomiting was the forceful expulsion of gastric contents from the mouth. Nausea and vomiting were evaluated on a 3-point ordinal scale (0=none, 1=nausea, 2=vomiting). The total incidence of nausea and vomiting was calculated. Metoclopramide 10 mg i.v. was available when vomiting occurred or on request. The proportion of parturients requiring rescue antiemetic in each group was recorded.

Pain intensity was assessed with a 10-cm visual analogue scale (VAS; 0=no pain, 10=most severe pain) and was recorded between 8:00 a.m. and 10:00 p.m. If parturients requested rescue analgesia for pain control, i.m. diclofenac 75 mg was available. Pruritus was assessed on a 3-point ordinal scale (0=none, 1=pruritus but only in a small area of the body, 2=generalized pruritus). Pruritus was treated with i.m. diphenhydramine (20 mg every 4 h as needed). Restlessness was also evaluated;[16] it was defined as a sensation of nervousness with an inability to keep still. Restlessness was treated with i.m. diphenhydramine 20 mg. The occurrence of any side-effect accompanying dexamethasone usage, such as wound infection or delayed wound healing, was recorded.

Sample size was predetermined.[24] We expected a 30% difference among groups in the proportion of parturients requiring rescue antiemetic for nausea and/or vomiting.[9–11] The α error was set at 0.05 (two-sided) and the β error at 0.10. The analysis showed that 37 parturients per group would be sufficient.[24] A series of one-way analyses of variance were conducted to examine differences among the three groups with respect to parametric variables. If a significant difference was found, the Bonferroni *t*-test was used to detect the intergroup differences. The Kruskal–Wallis test was used to determine differences among the three groups with respect to non-parametric variables, and was followed by the Mann–Whitney rank-sum test for intergroup differences. Categorical variables were analysed with a series of 3×2 χ^2 tests to determine differences among the three groups, followed by a 2×2 χ^2 test for intergroup differences. All follow-up analyses were corrected for the number of simultaneous contrasts using Bonferroni adjustment. A *P* value less than 0.05 was considered significant.

Results

Of the 120 parturients enrolled, seven were withdrawn because of failure of epidural catheterization before surgery. Therefore, 113 parturients completed the trial. There was no significant difference among groups with respect to age, weight, height, parity, duration of anaesthesia and surgery, and lignocaine consumption during surgery (Table 1).

After surgery, all parturients received epidural morphine for postoperative pain relief. During the 24-h observation period, 8 parturients in the dexamethasone group and 9 and 11 in the droperidol and saline groups respectively requested rescue analgesia (i.m. diclofenac 75 mg). The number of diclofenac injections was 10 in the dexamethasone group, and 11 and 14 in the droperidol and saline groups respectively. The median time until rescue analgesia was 16 h in the dexamethasone group and 14 h in both the droperidol and the saline group. The differences in the above variables among groups were not significant. All parturients reported low VAS pain scores (0–3) and the differences among groups were not significant.

The total incidence of nausea and vomiting was 18% in the dexamethasone group and 21% in the droperidol group, in comparison with 51% in the saline group (*P*<0.01 and *P*<0.05 respectively) (Table 2). The proportions of

Table 1 Patient characteristics Values are median (range)

Characteristic	**Group**		
	Dexamethasone (*n*=38)	**Droperidol** (*n*=38)	**Saline** (*n*=37)
Age (yr)	31 (20–35)	33 (23–35)	32 (21–35)
Weight (kg)	70 (52–86)	72 (52–89)	71 (51–88)
Height (cm)	158 (140–172)	158 (143–174)	157 (142–176)
Parity	2 (1–3)	2 (1–3)	2 (1–3)
Duration of anaesthesia (min)	64 (48–83)	58 (49–84)	61 (52–87)
Duration of surgery (min)	52 (34–69)	48 (38–70)	46 (38–71)
Lignocaine consumption (mg)	340 (300–420)	320 (300–400)	340 (300–420)

Table 2 Incidence of side-effects related to epidural morphine and the proportion of parturients requiring rescue antiemetic. Data are numbers of patients (%) with symptoms in a 24 h observation period $^{*}P<0.05$, $^{**}P<0.01$ compared with saline group, using a 3×3 χ^2 test followed by a 2×2 χ^2 test

Side-effect	Group		
	Dexamethasone (n=38)	Droperidol (n=38)	Saline (n=37)
Nausea/vomiting			
Nausea	4 (11)	5 (13)	11 (30)
Vomiting	3 (8)	3 (8)	8 (22)
Total	7 (18)**	8 (21)*	19 (51)
Patients requiring rescue antiemetic	4 (11)*	5 (13)*	15 (41)
Pruritus			
Pruritus but only in a small area of the body	12 (32)	12 (32)	12 (32)
Generalized pruritus	5 (13)	4 (11)	5 (14)
Total	17 (45)	16 (42)	17 (46)

parturients who required rescue antiemetic (metoclopramide) were 11% in the dexamethasone group and 13% in the droperidol group, in comparison with 41% in the saline group ($P<0.05$) (Table 2).

The incidence of pruritus was similar among groups (45% in the dexamethasone group, 42% in the droperidol group and 46% in the saline group) (Table 2). Six parturients (16%) in the droperidol group reported restlessness. No parturient in the other two groups reported this ($P<0.05$). No parturient reported wound infection or delayed wound healing.

Discussion

In the present study we found that the total incidence of nausea and vomiting after epidural morphine was 51% when no antiemetic was given prophylactically. After pretreatment with either dexamethasone or droperidol, the total incidence of nausea and vomiting was significantly reduced. Both dexamethasone and droperidol were effective in preventing epidural morphine-related nausea and vomiting in parturients undergoing Caesarean section. However, those who received droperidol reported a higher incidence of restlessness.

Dexamethasone is effective in preventing nausea and vomiting associated with chemotherapy.[12 13] Recently, dexamethasone has also been reported to be effective in preventing PONV in patients undergoing tonsillectomy, thyroidectomy, cholecystectomy and hysterectomy.[17 20–23] In a previous study, we also found that dexamethasone is effective in preventing nausea and vomiting associated with epidural morphine in patients undergoing abdominal hysterectomy.[11] Because of these data, we hypothesized that dexamethasone might also be effective in preventing nausea and vomiting after epidural morphine for analgesia after Caesarean section.

The exact mechanism by which dexamethasone, a glucocorticoid, exerts an antiemetic action after epidural morphine is not known. Glucocorticoids have been shown to have various effects on the central nervous system; they regulate transmitter levels, receptor densities and neurone configuration.[25 26] Numerous glucocorticoid receptors are found in the nucleus of the solitary tract, the nucleus of raphe and the area postrema.[26 27] These nuclei are well known to have significant neuronal activity in the regulation of nausea and vomiting.[10 19] Dexamethasone may exert its antiemetic action through these nuclei.

We also found that dexamethasone did not influence the efficacy of epidural morphine-related analgesia. Parturients in the three groups required similar amounts of rescue analgesic and reported similar intensities of postoperative pain. Also, i.v. dexamethasone did not influence the occurrence of pruritus related to epidural morphine for post-Caesarean section analgesia.

A wide dose range of dexamethasone (8–32 mg) has been used in the management of PONV and emesis associated with chemotherapy.[12–15 17–23] A dose of 8–10 mg has been used most frequently in the prevention of PONV.[17 20 23] For example, an 8 mg dose of dexamethasone was effective in the prevention of nausea and vomiting after epidural morphine in patients undergoing abdominal hysterectomy.[11] Therefore an 8 mg dose was chosen in this study. However, dose–response studies are needed to determine the optimal dose of dexamethasone.

The long-term administration of corticosteroids is associated with side-effects, such as increased risk of infection, delayed wound healing, glucose intolerance and adrenal suppression. However, we were unable to find a report of these adverse effects related to a single dose of dexamethasone, and delayed wound healing or wound infection did not occur in our study. Although a single dose of dexamethasone is considered safe, further study is indicated.

Droperidol also has a potent antiemetic effect.[28 29] Previous studies have demonstrated that its antiemetic effect is equal to that of ondansetron and superior to that of metoclopramide in preventing PONV.[28 29] The recommended dose for this purpose is 1.25 mg.[29] In our study, we also found that droperidol 1.25 mg is effective in preventing nausea and vomiting related to epidural morphine for post-Caesarean section analgesia. However, droperidol is not devoid of side-effects. Restlessness, a common droperidol-related side-effect, was found in 16% parturients who received droperidol 1.25 mg in our study. Although this side-effect was relieved by the i.m. diphenhydramine, it nevertheless produced mental distress in our patients. Because dexamethasone demonstrated a significant antiemetic effect without evident adverse effects, it may be a valuable treatment for the prophylaxis of epidural morphine-related nausea and vomiting in parturients receiving Caesarean section.

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LABORATORY INVESTIGATIONS

Central cholinergic depletion induced by 192 IgG-Saporin alleviates the sedative effects of propofol in rats

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We examined the effect of central cholinergic depletion on the sedative potency of propofol in rats. Depletion was produced by intracerebroventricular administration of an immunotoxin specific to cholinergic neurones (192 IgG-Saporin; 2 µg). As a result of this lesion, acetylcholine concentration was reduced by about 40% in the frontoparietal cortex and in the hippocampus but was essentially normal in the striatum and cerebellum. Sedation in rats was assessed as the decrease in locomotor activity. Sedative potency of propofol (30 mg kg^{-1} i.p.) was reduced by about 50% in rats who received the injection of 192 IgG-Saporin as compared to controls. These results show that a central cholinergic depletion alleviates the sedative effect of propofol, and indicates that basal forebrain cholinergic neurones might mediate part of the sedative/hypnotic effects of propofol.

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The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain, and has long been recognized as playing a key role in the regulation of consciousness.[1 2] Briefly, the cholinergic system is distributed in a variety of different nuclei of which two groups (basal-forebrain and pedunculopontine) have extensive projections to the cortex and thalamus. Pedunculopontine cholinergic neurones are considered to control rapid eye movement sleep or dreaming, while basal-forebrain cholinergic pathways appear to generate and integrate conscious awareness.

Cellular and molecular studies suggest that cholinergic neurotransmission is a potential mediator of general anaesthetic actions.[3–5] It has been largely suggested that some anaesthetics produce their effects via actions on both muscarinic and nicotinic receptors. In this respect, propofol (2,6-diisopropylphenol), an intravenous general anaesthetic, has been shown to directly act on nicotinic acetylcholine receptors, more precisely on the subtype of nicotinic receptors found in the central nervous system ($\alpha 4\beta 2$).[6–8] Propofol also has dose-dependent inhibitory effects on acetylcholine release in the frontal cortex and hippocampus, as shown by *in vivo* microdialysis in the rat brain.[9 10] Though there are some reports of the effects of propofol on cholinergic neurotransmission, to date there is no clinical and/or physiological evidence that an inhibitory effect on cholinergic function may be involved in the sedative/hypnotic effects of propofol.

To what extent cholinergic neurons mediate the hypnotic effects of propofol, is of particular relevance to the effects of anaesthetics in aged patients. There is evidence for an impairment of cholinergic function in normal as well as in neuropathological ageing,[11–14] but little is known about any age-related modification of anaesthetic effects in the central nervous system.[10] Thus an investigation of the interactions between anaesthetics and cholinergic lesions seems worthwhile, particularly if one considers the effects of anaesthetics may depend upon age.

We therefore wondered to what extent the cholinergic system may be involved in propofol-induced sedative/hypnotic effects. To address this question, we assessed the effect of central cholinergic depletion on the sedative effect of propofol in rats. Cholinergic depletion was performed by intracerebroventricular (ICV) administration of 192 IgG-

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Saporin, a monoclonal antibody to the p75NGF receptor coupled to the ribosomal toxin saporin. This neurotoxin is selective for cholinergic neurons of the basal forebrain.[15–19] Using a locomotor activity test, we measured the sedative potency of propofol in lesioned rats as compared to controls. The extent of the cholinergic damage was assessed by measuring acetylcholine concentrations in various regions of the brain.

Methods

All procedures involving animals and their care were conducted in accordance with the institutional guidelines that are in compliance with national (concil directive #87848, October 19, 1987, Ministère de l'Agriculture et de la Forêt, Service Vétérinaire de la Santé et de la Protection Animales; permission #6212 to J-C. Cassel) and international (NIH publication, N°86–23, revised 1985) laws and policies.

Materials

Animals
We used 16 female Long Evans rats (Janvier, France) that weighed 200–210 g. They were housed in a colony room maintained on a 12:12 h dark-light cycle (lights on at 7:00 AM), with food and water provided *ad libitum*. The colony and testing rooms were temperature controlled (21°C).

Drugs
Propofol (10 mg ml^{-1}, Diprivan; Zeneca, Paris, France) was dissolved in 10% intralipid. Drugs were prepared immediately before use and injected intraperitoneally (i.p.) in a volume of 3 ml kg^{-1}.

Apparatus
Eight identical activity cages (size, 45 × 30 ×30 cm) were used. Each cage had an infrared detector (IPR124, Talco, Paris, France) placed behind a Fresnel lens and located at the roof of the cage, which allows monitoring of animal movement in different sections of the cage. The signal was fed into a computer that summed all horizontal movements (one unit representing one crossing from one section to the other) during three consecutive periods of 5 min.

Study design
Rats were randomly allocated to two groups as follows: rats with saporin lesions (SAPO; n=8) and sham-operated controls (SHAM; n=8). During surgery, the rats received ICV infusions of 192 IgG-Saporin to induce a cholinergic depletion (SAPO), or vehicle (SHAM). The sedative effect of propofol (30 mg kg^{-1}, intraperitoneally) was measured using a crossover behavioural experiment that measured locomotor activity. Finally the extent of the cholinergic depletion was assessed neurochemically by determining the concentration of acetylcholine in the frontoparietal cortex, hippocampus, striatum and cerebellum.

Surgery
All surgical procedures[19] were conducted under aseptic conditions, using equitesin (composed of pentobarbital, chloral hydrate and alcohols) anaesthesia (3.0 ml kg^{-1}, i.p.). Following a mini-craniotomy, injections into the lateral ventricles were performed stereotaxically using a 2-µl Hamilton syringe at the following co-ordinates (in mm): A: –0.8 (from Bregma), L: ±1.4 (from midline); V: –4.3 (from Bregma), with the incisor bar set at the level of the interaural line. Following injection, the needle was left *in situ* for 5 min, retracted over 2 mm, and maintained there for another 4 min before complete retraction. Rats with saporin lesions received an ICV injection of 2 µg of the immunotoxin 192 IgG-Saporin (2 µg per rat; 1 µl per lateral ventricle, concentration 1 µg μl^{-1} of phosphate-buffered saline). In the control group, rats were treated in a similar manner, except that phosphate-buffered saline was injected in place of 192 IgG-Saporin.

Behavioural experiment
Propofol-induced sedation was assessed as follows:[20 21] the rat was placed in an activity cage with its horizontal movements being recorded using a detector located at the top of the cage. When placed in such a cage, undrugged rats exhibited a locomotor activity aimed at exploring which decreased progressively over time. Activity counts expressed as metric units explored per 5 min were used as activity scores. The experiment was performed over 2 days. The first day, half the rats of each group were injected intraperitoneally with propofol (30 mg kg^{-1}), the remainder injected with vehicle. All rats were then returned to their home cage. Ten minutes later, each rat was placed in one of the eight experimental cages and tested for 15 min. During the test, locomotor activity was recorded during three consecutive periods of 5 min, abbreviated T1, T2 and T3 hereafter. The second day, the procedure was reversed (vehicle instead of propofol, and *vice versa*).

Comparison of the activity scores found after the injection of vehicle in rats with saporin lesions with those of sham-operated controls allowed assessment of the effect of the cholinergic lesion. Comparison of the activity scores found after propofol injection with those after vehicle allowed determination ofthe effects of the cholinergic lesion on the sedative potency of propofol. Sedative potency was calculated for each rat as follows: (activity score after vehicle injection *minus* activity score after propofol injection)/(activity score after vehicle injection *plus* activity score after propofol injection).

Neurochemical control

To control for the efficiency of the cholinergic lesions, six rats of each group (SHAM or SAPO) were arbitrarily chosen by an experimenter who was unaware of the rats' activity scores. These were killed by microwave irradiation in order to inactivate brain enzymes such as acetylcholinesterase.

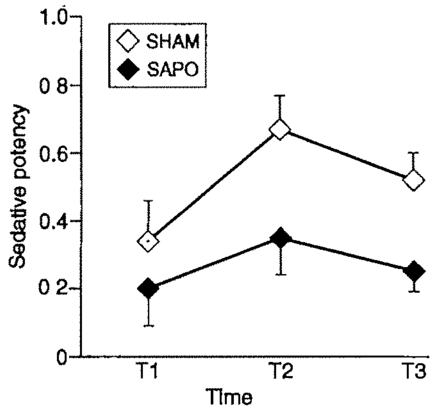

Fig 1 Sedative potency of propofol 30 mg kg^{-1} i.p. (T1 10–15 min, T2: 15–20 min, T3: 20–25 min, after the injection) in rats who received intraventricular injections of.2 μg of 192 IgG-Saporin (SAPO) or of 2 μl of phosphate-buffered saline solution (SHAM). Sedative potency was expressed as the ratio: (activity score after vehicle injection *minus* activity score after propofol injection)/(activity score after vehicle injection *plus* activity score after propofol injection). Results are expressed as mean±SEM.

Following decapitation, the brain was extracted and dissected on a cold plate in order to separate the striatum, frontoparietal cortex, and hippocampus. The hippocampus was further split into its dorsal and ventral areas. Left and right structures from each rat were pooled, weighed and maintained at −80°C until neurochemical determination.

To determine acetylcholine concentrations by high performance liquid chromatographic analysis, tissue samples were homogenized in 1 N formic acid/acetone (18/8.5, vol./vol.). Formic extracts were then purified by a tetraphenylboron exchange of amines in 3-heptanone, followed by 0.1 N HCl extraction. High performance liquid chromatographic analysis was performed on a C(18)Spherisorb ODS2 reverse phase column (3 μm pore size, 7 mm in diameter, 10 cm long). The mobile phase consisted of 0.05 M KH_2PO_4, pH=7, containing 600 mg litre^{-1} of tetramethylammonium chloride and 25 mg litre^{-1} sodium octane sulphate. The flow rate was 0.8 ml min^{-1}. Acetylcholine was converted into betaine in a post-column reactor with covalently bound acetylcholinesterase and choline oxidase. The resulting hydrogen peroxide was detected using a 50740 ESA cell working electrode at 0.3 V.

Statistical analysis

For behavioural experiments, two dependent variables were used: activity score after vehicle injection and sedative potency of propofol. Statistical analyses of these variables were performed using analysis of variance with repeated measures (between factor: SHAM or SAPO, within factor: time). For neurochemical control, one way analyses of variance as performed on acetylcholine concentration in the different brain structures, namely hippocampus (dorsal and ventral), frontoparietal cortex, striatum and cerebellum. $P<0.05$ was considered indicative of statistical significance.

Results

Following injection of vehicle alone, the absolute activity scores decreased progressively in both groups during the test (activity scores, mean (SEM); T1: 306 (20) *vs.* 278 (12); T2: 240 (21) *vs.* 249 (24); T3: 189 (15) *vs.* 193 (24), for groups SHAM and SAPO, respectively). Analysis of variance showed a significant effect of the Time ($P<0.05$), but no effect of Group, SHAM or SAPO ($P=0.83$).

The sedative potency of propofol (30 mg kg^{-1} i.p.) was significantly decreased in SAPO, as compared to SHAM rats (Figure 1). The time course of the sedative effect appeared similar in both groups. Analysis of variance showed a significant effect of Group, SAPO or SHAM, but no statistical significant effect of Time nor interaction between Group and Time (Group, $P<0.05$; Time, $P=0.07$; Group×Time, $P=0.67$).

Acetylcholine concentrations were significantly reduced in the frontoparietal cortex and hippocampus for SAPO, as compared to SHAM rats (all $P<0.05$) (Table 1). Acetylcholine concentrations in the striatum and cerebellum were not significantly altered by 192 IgG-Saporin (striatum, $P=0.62$; cerebellum, $P=0.68$).

Discussion

In the present study we report for the first time that cholinergic neurotransmission may be involved in the sedative effects of propofol.

To our knowledge, we show for the first time that cholinergic depletion in the basal forebrain alleviates the sedative effect of propofol in rats. Indeed, the activity found after propofol treatment was significantly less in rats which had sustained ICV injection of 192 IgG-Saporin than in controls. Sedative potency of propofol was decreased by about 50% but the time-course of the sedative effect appeared unchanged (Fig. 1). This finding cannot be attributed to the pre-existence of impaired locomotion due to 192 IgG-Saporin, as the activity scores following injection of vehicle were comparable in the experimental and control groups. Evidence that 192 IgG-Saporin induced cholinergic depletion in the basal forebrain is substantiated by reduced acetylcholine concentration in the hippocampus and frontoparietal cortex (Table 1). From previous experiments using intraventricular administration of 192 IgG-Saporin, it is known that the extent of cholinergic depletion depends on the amount of 192 IgG-Saporin injected. Close-to-maximum effects are generally obtained with about 5 μg.[22] In our study, the reduction of acetylcholine concentration was about 40%. Importantly for locomotion and movement, the concentration of acetylcholine in the striatum was unchanged, an observation which is in line

Table 1 Mean concentrations of acetylcholine in various brain structures of rats who received intraventricular injections of 2 μg of 192 IgG-Saporin (SAPO) or of 2 μl of a phosphate-buffered saline solution (SHAM). All data are given in ng/mg microwaved tissue. Values in parentheses correspond to SEM $^*P<0.05$ *vs* SHAM

	Acetylcholine concentration (ng mg^{-1})	
	SHAM	**SAPO**
Dorsal hippocampus	0.67 (0.04)	0.40 (0.02)*
Ventral hippocampus	0.76 (0.07)	0.41 (0.04)*
Fronto-parietal cortex	0.29 (0.03)	0.17 (0.03)*
Striatum	2.31 (0.07)	2.44 (0.15)
Cerebellum	0.24 (0.03)	0.25 (0.01)

with previous reports.[22,23] Similarly, the concentration of acetylcholine in the cerebellum was not significantly affected by 192 IgG-Saporin.

How might a depletion of basal forebrain cholinergic neurons alleviate the depressant effect of propofol on the central nervous system? Physiological studies have highlighted the role of cholinergic neurotransmission in the maintenance of consciousness.[1,2] Depending on the brain area, cholinergic neurotransmission exerts either an excitatory or an inhibitory role on consciousness. For example, small amounts of acetylcholine injected into the tegmental reticular formation cause sleep whereas infusions of acetylcholine in the region of the amygdala, septum or hippocampus stimulate arousal behaviour.[24] From our results, it is clear that the basal forebrain cholinergic system participates in propofol-induced sedation although its alteration has no major effect on exploratory activity in our experimental conditions. We suggest that propofol depresses central nervous system excitability by a mechanism that probably involves, at least in part, inhibition of the excitatory effect of the basal forebrain cholinergic system associated with the maintenance of consciousness. However, it is generally accepted that propofol acts as a potent gamma-aminobutyric acid (GABA) agonist. Propofol potentiates the inhibitory actions of the GABA_A receptor and its pharmacological mechanisms have been investigated in some detail.[25–27] Using *in vivo* microdialysis, Kikuchi *et al.*[9] have shown that the inhibitory effects of propofol on acetylcholine release is mediated by GABA_A receptors in the frontal cortex and in the hippocampus in rats. Because propofol acts directly on ligand-gated ion channels of GABA_A and neuronal nicotinic receptors, the mechanisms by which the hypnotic effects of propofol occur may involve an inhibition of specific neuronal acetylcholine receptors in addition to an interaction with GABA_A receptors implicated in the modulation of the activity of cholinergic neurons.

The interaction between propofol and central cholinergic function is of great interest in investigations of the mechanisms which underlie the age-dependent effects of propofol. Recent experimental studies showed that brain sensitivity to propofol can be modified by ageing.[10,28,29] In particular, the anaesthetic potency of propofol appears reduced by ageing, independently of any pharmacokinetic modifications. Larsson and Wahlstrom[29] demonstrated that brain concentrations of propofol need to be increased in aged as compared to young rats, in order to obtain the same depressant effect of propofol on electroencephalographic parameters. As previously mentioned, central cholinergic function is impaired by normal ageing.[11–14] For example, in the aged brain cholinergic markers such as the activity of choline acetyltransferase and the levels of hemicolinium-3 binding are reduced in the medial septum, the hippocampus and the cingulate cortex.[13] Similarly, the biosynthesis of nicotinic receptors is reduced by ageing as shown by a 30–50% reduction of mRNA levels in the brain of 29- to 32-month-old rats.[12] Because ageing alters cholinergic function and in the light of our present findings, one could hypothesise that the weaker potency of propofol to induce sedative/hypnotic effects in the aged subjects is due to the alteration of cholinergic function.

In summary, our study shows that the sedative effect of propofol is partly mediated by cholinergic mechanisms and can be attenuated by an alteration of cholinergic function in the basal forebrain. This finding points towards a key role of cholinergic mechanisms in the effects of propofol. Moreover, our results support the working hypothesis that the ageing process might reduce the brain sensitivity to propofol due to age-related changes in cholinergic function. To what extent this could apply to the anaesthetic effect of propofol or of other anaesthetics needs further investigation.

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Inhibitory effects of intravenous anaesthetic agents on K^+-evoked norepinephrine and dopamine release from rat striatal slices: possible involvement of P/Q-type voltage-sensitive Ca^{2+} channels

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The role of the voltage-sensitive Ca^{2+} channel (VSCC) as a target for anaesthetic action remains controversial. In this study we characterized the VSCC subtypes involved in K^+-evoked norepinephrine and dopamine release from rat striatal slices and used this model system to examine the effects of a range of i.v. anaesthetics on release. Nifedipine (L-channel-selective), ω-conotoxin GVI_A (N-channel-selective), ω-agatoxin IV_A (P-channel-selective), ω-conotoxin $MVII_C$ (P/Q-channel-selective) and Cd^{2+} (non-selective), along with alphaxalone, propofol and ketamine, were used in various combinations. ω-Agatoxin IV_A, ω-conotoxin $MVII_C$ and Cd^{2+} fully (100%) inhibited norepinephrine and dopamine release. Clinically achievable concentrations of alphaxalone inhibited norepinephrine and dopamine release, with concentrations producing 25 and 50% inhibition (IC_{25} and IC_{50}) of the maximum of 2.1 and 7.8 μM respectively for norepinephrine and 2.9 and 7.2 μM for dopamine. The effects of propofol were observed at the top of the clinical range and those of ketamine exceeded this range. In addition, IC_{50} values for alphaxalone in the presence and absence of nifedipine and ω-conotoxin GVI_A did not differ from the control. Our data suggest that clinically achievable concentrations of alphaxalone and propofol inhibit norepinephrine and dopamine release, which is mediated predominantly through P/Q-type VSCCs, suggesting a role for these channels in anaesthetic action.

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Since Nowycky, Fox and Tsien classified neuronal voltage-sensitive Ca^{2+} channels (VSCCs) into types T, L and N, at least six classes of VSCC have been described (T, L, N, P, Q, R).[1] It is clear that Ca^{2+} has an important role to play in neuronal signalling as this divalent cation contributes to the regulation of neuronal excitability and neurotransmitter release predominantly via the action of VSCCs.[2] Of these, the L-type VSCC is located predominantly on neuronal cell bodies, is sensitive to dihydropyridines (DHPs) and may modify neurotransmitter release under certain circumstances.[3] N-type VSCCs are distributed widely in the nervous system, are sensitive to ω-conotoxins and are involved in the regulation of neurotransmitter release.[2 4] P-type VSCCs are also widely distributed in the central nervous system and account for 80% of the VSCCs present in mammalian nerve terminals.[5] This type of channel is involved in central synaptic transmission[5–8] and is blocked by ω-agatoxin IV_A. Q-channels are closely related to the P-channels, but display lower sensitivity to ω-agatoxin IV_A (although this toxin does block Q-channels at higher concentrations).

The molecular target site(s) for anaesthetic action remains to be determined. Whilst it is generally accepted that the $GABA_A$ receptor represents an important target site,[9–11] there is evidence for depressed excitatory transmission[12 13] and actions at VSCCs.[14 15] We have previously shown that a range of i.v. anaesthetic agents (with the exception of ketamine) inhibit the binding of DHPs to L-VSCC and that there is a significant correlation between binding affinity and the peak plasma concentrations seen during anaesthesia.[16] Whilst radioligand binding studies give important information about whether an interaction occurs, these studies give little indication about the functional consequences of such an interaction. Clearly, more functional studies are required.

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This study had two main aims: (i) to define the VSCC subtype(s) controlling norepinephrine and dopamine release from rat striatal slices, and (ii) to examine the interaction of i.v. anaesthetic agents on this response in a more intact slice model. We examined the effects of nifedipine (L-channel-selective), ω-conotoxin GVI_A (N-channel-selective), ω-agatoxin IV_A (P-channel-selective), ω-conotoxin $MVII_C$ (P/Q-channel-selective) and Cd^{2+} (non-selective) on K^+-evoked norepinephrine and dopamine release from rat striatal slices. We also examined the effects of the i.v. anaesthetic agents alphaxalone, propofol and ketamine on these responses. We should emphasize that we do not claim that inhibition of norepinephrine and dopamine release from the striatum is responsible for the anaesthetic state (although this is possible); we used this model system to study any role of VSCC in the actions of three i.v. anaesthetic agents.

Methods

Materials and stock solutions

ω-Conotoxin GVI_A, ω-agatoxin IV_A and ω-conotoxin $MVII_C$ were purchased from the Peptide Institute (Osaka, Japan). Nifedipine was purchased from Wako (Osaka, Japan), pargyline, nomifensin and i.v. anaesthetic agents were from Sigma-Aldrich Japan (Tokyo, Japan), and HEPES from Dojin Laboratories (Kumamoto, Japan). All other chemicals used were of the highest quality available. Stock solutions were made as follows: pure propofol (100 mM stock in dimethyl sulphoxide, DMSO); alphaxalone and nifedipine (50 mM stock in DMSO), ketamine and $CdCl_2$ (100 mM stock in distilled water); and ω-conotoxin GVI_A, ω-conotoxin $MVII_A$ and ω-agatoxin IV_A (10^{-4} M in distilled water). All agents were then diluted in Krebs–Ringer bicarbonate buffer; the highest anaesthetic concentration used was limited by agent solubility.

Preparation of slices

Male Wistar rats (250–300 g) were decapitated and their brains were quickly removed and immersed in ice-cold Krebs–Ringer bicarbonate buffer solution (KRBS) of the following composition (mM): NaCl 133, KCl 4.8, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 1.5, glucose 11.1, HEPES 10 (pH 7.4). Striatal tissue was dissected and cross-chopped using a tissue chopper to produce slices of 350×350 μm. The slices were then washed three times in ice-cold KRBS and transferred (1 ml aliquots of slices, equivalent to about 6 mg protein) to polypropylene tubes. Striatal slices from one rat were used for one experiment (i.e. one concentration–response curve was constructed for each agent).

Norepinephrine and dopamine release experiments

After the supernatant had been discarded, the slices were resuspended in 1 ml of fresh KRBS and incubated for 10 min at 37°C. This procedure was repeated to obtain a stable baseline. Immediately after this second incubation, the slices were resuspended (1 ml KRBS) and incubated for 0–9 min in the absence (basal release) and presence (evoked release) of 40 mM KCl. In some experiments, slices were incubated for a fixed time of 6 min with KRBS containing 0–70 mM KCl in order to obtain a K^+-evoked release concentration–response curve. All buffers used in release studies contained the monoamine oxidase inhibitor pargyline (10 μM), and the reuptake inhibitor nomifensin (10 μM) to amplify the release signal by preventing amine breakdown and reuptake respectively. In addition, for samples containing K^+, an equal concentration of Na^+ was removed.

Effects of VSCC blockers and i.v. anaesthetics on K^+-evoked norepinephrine and dopamine release

Slices were prepared and incubated as above. They were resuspended in 1 ml KRBS containing nifedipine (10^{-11} to 10^{-6} M), ω-conotoxin GVI_A (10^{-11} to 10^{-6} M), ω-agatoxin IV_A (3×10^{-9} to 10^{-6} M), ω-conotoxin $MVII_C$ (3×10^{-9} to 10^{-6} M) and Cd^{2+} (10^{-6} to 3×10^{-4} M), alphaxalone (10^{-8} to 10^{-4} M), propofol (10^{-8} to 10^{-3} M) and ketamine (10^{-8} to 10^{-3} M) in various combinations and incubated for a further 10 min at 37°C. This procedure was repeated. Six minutes of basal sampling was then performed before the slices were finally exposed to 40 mM K^+ for 6 min in the continued presence of the test agents as appropriate.

To examine whether the inhibitory effects of alphaxalone on norepinephrine and dopamine release are mediated mainly via P and Q-VSCCs, KRBS contained various concentrations of alphaxalone and 40 mM K^+ with or without nifedipine (10^{-6} M) and ω-conotoxin GVI_A (10^{-6} M).

Measurement of norepinephrine and dopamine release

Monoamine contents in the release samples were determined directly by high-performance liquid chromatography with an electrochemical detector (Model 5100A, ESA Coulochem) as described by Takeda and colleagues.[17] Aliquots (20 μl) of acidified (perchloric acid) release samples were injected onto a reverse-phase column (C18, 4.6×150 mm; MC Medical, Tokyo, Japan). For each experimental run, a standard curve for norepinephrine and dopamine was constructed (using 3,4-dihydroxybenzylamine as the internal standard). The intra-assay coefficient of variation was 3.3% for norepinephrine and 6.5% for dopamine.

Calculations and data analysis

All data are presented as mean (SEM) (n). The concentrations of VSCC blockers and anaesthetic agents producing 25% (IC_{25}) and 50% (IC_{50}) inhibition were estimated from individual curves by non-linear regression analysis

(Graphpad-Prism v. 2.0). When appropriate, statistical analysis was by repeated measures ANOVA and the unpaired *t*-test for intra- and inter-group comparison respectively. $P<0.05$ was considered significant.

Results

Norepinephrine and dopamine release evoked by K^+ was time-dependent, reaching a maximum some 6–7 min after stimulation (Table 1). In addition, K^+ produced concentration-dependent release of norepinephrine and dopamine, with pEC_{50} values of 1.41 (0.02) (38.8 mM) and 1.46 (0.03) (34.9 mM) respectively (Fig. 1).

Effects of VSCC blockers on neurotransmitter release

The non-selective VSCC antagonist Cd^{2+} completely abolished norepinephrine and dopamine release (Fig. 2A). In addition, selective VSCC antagonists also reduced release to varying degrees (Fig. 2B–E, Table 2). L-VSCC blockade with nifedipine (Fig. 2B) produced only a 15–20% inhibition of release ($P<0.01$). N-VSCC blockade (Fig. 2C) also produced a small but significant inhibition of release ($P<0.01$). In contrast, blockade of P/Q VSCC (Fig. 2D and E) produced a marked inhibition of release.

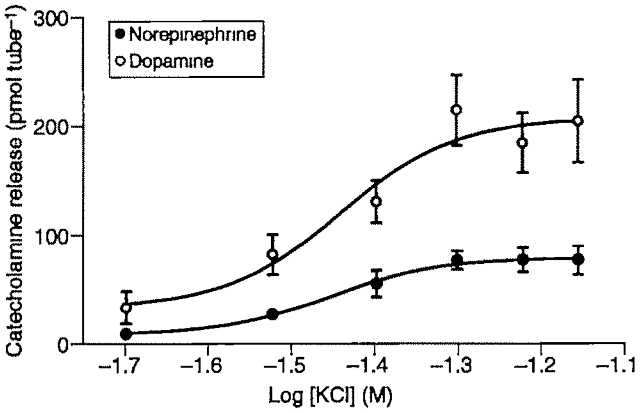

Fig 1 K^+-evoked norepinephrine and dopamine release from rat striatal slices is concentration-dependent. Concentrations producing 50% of the maximum response (IC_{50}) were 38.8 and 34 9 mM for norepinephrine and dopamine respectively. Data are mean (pg ml^{-1}) and SEM (n=4).

Effects of i.v. anaesthetics on neurotransmitter release

Alphaxalone produced concentration-dependent and full inhibition of norepinephrine and dopamine release (Fig. 3, Table 3). In addition, dose–response curves for the inhibition of norepinephrine and dopamine release by alphaxalone in the presence and absence of L- and N-type VSCC blockers coincided (Fig. 4). The pIC_{50} values (mean IC_{50}) for the inhibition of norepinephrine and dopamine release by alphaxalone in the presence of nifedipine and ω-conotoxin GVI_A (5.11 (0.11) (7.8 μM) and 5.22 (0.08) (6.1 μM) respectively) were similar to those in the absence of nifedipine and ω-conotoxin GVI_A (Table 3).

The inhibitory effects of propofol were weaker than those of alphaxalone, and these did not saturate at the highest concentration used. Curve fits for propofol and ketamine were poor because of this lack of saturation, and therefore the estimated IC_{25} and IC_{50} values should be interpreted with caution. Notwithstanding, the estimated IC_{25} values for the inhibition of norepinephrine and dopamine release by propofol were close to the total plasma concentrations seen during anaesthesia (although the free concentration would be lower) (Fig. 3, Table 3). In contrast, the effects of ketamine on norepinephrine and dopamine release occurred at concentrations in excess of those encountered clinically (Fig. 3, Table 3).

Table 1 Time course of K^+-evoked norepinephrine and dopamine release Mean of two measurements, expressed as pmol $tube^{-1}$; each tube contained 1 ml of sample and about 6 mg protein

	Time (min)								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Norepinephrine (pmol)	19 0	24.8	27.7	36 0	35 1	41.5	37.9	39.5	37.6
Dopamine (pmol)	66.8	80 5	112.2	136 2	124.9	128.8	133 5	113 7	112.7

Table 2 pIC_{50} (mean IC_{50}, maximum inhibition) of VSCC antagonists for K^+-evoked norepinephrine and dopamine release. Data are mean (SEM)

	VSCC antagonist				
	Cd^{2+}	**Nifedipine**	**ω-Conotoxin GVI_A**	**ω-Agatoxin IV_A**	**ω-Conotoxin $MVII_C$**
Norepinephrine	4 83 (0.04) (14 8 μM, 98%)	8.32 (0.26) (4.78 nM, 20%)	8 10 (0 05) (7.94 nM, 35%)	6.89 (0 11) (129 nM, 88%)	6.71 (0 14) (195 nM, 100%)
Dopamine	4.84 (0.01) (14 5 μM, 95%)	8 55 (0.40) (2.82 nM, 15%)	8 42 (0 24) (3.80 nM, 33%)	6.88 (0.07) (131 nM, 88%)	6.96 (0 10) (109 nM, 100%)

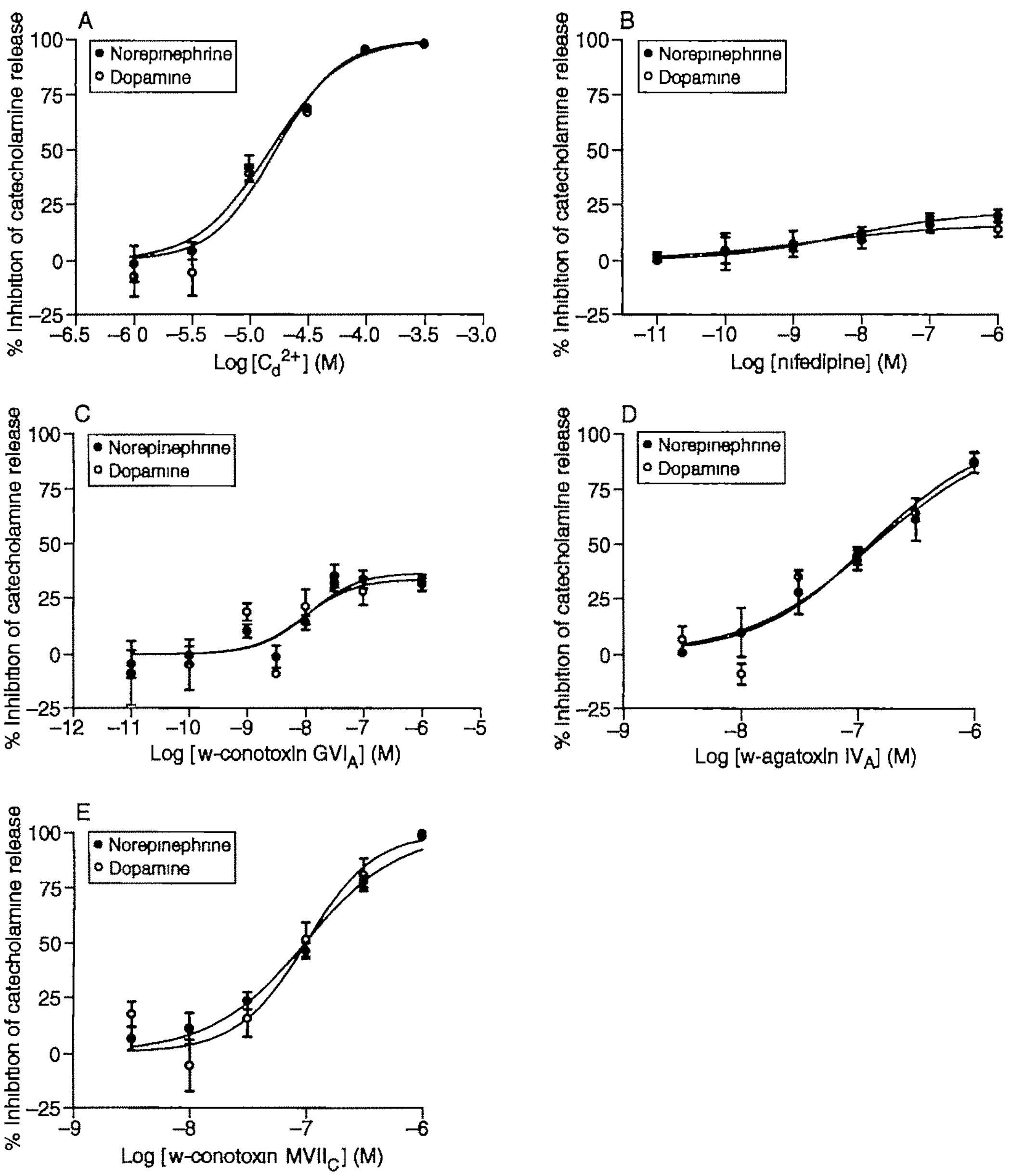

Fig 2 Effects of Ca^{2+} channel blockers Cd^{2+} (A, non-selective), nifedipine (B, L type), ω-conotoxin GVIA (C, N type), ω-agatoxin IV_A (D, P type), and ω-conotoxin $MVII_C$ (E, P/Q type) on K^+-evoked norepinephrine and dopamine release Data are mean and SEM (n=6).

Discussion

Consistent with previous reports,[18 19] neurotransmitter release evoked by K^+ (depolarization) was time- and concentration-dependent. Although Harvey and colleagues[19] showed that the response to K^+ differed for each neurotransmitter, dopamine and norepinephrine showed similar responses in the present study. Harvey and colleagues[19] demonstrated that internal calcium is unlikely to be involved in the release of these catecholamines from brain slices. It was concluded that K^+-evoked dopamine and norepinephrine release are mediated predominantly by VSCCs, and the same argument can be applied to our data. However, there are preparations in which the release of internal stored Ca^{2+} is capable of supporting release, albeit to a lesser extent. For example, we have shown that carbachol (acting via the M_3 muscarinic receptor) is capable of eliciting norepinephrine release from SH-SY5Y human neuroblastoma cells in the absence of external Ca^{2+}, implying that the release of stored Ca^{2+} evokes transmitter release.[20]

Nifedipine, an L-type VSCC blocker, inhibited dopamine and norepinephrine release from rat striatal slices by 15–20%. The IC_{50} of nifedipine is consistent with the K_i of this agent for the displacement of [^{3}H]PN200–110 binding to rat striatal membranes reported previously.[21] The release of dopamine and norepinephrine from rat brain slices has been reported to be mediated partially through N-type, but more markedly through P/Q-type VSCCs.[4 18 19 22 23] In agreement with these reports, the present study also showed that the inhibition of catecholamine release by the range of selective VSCC blockers studied was similar to that reported previously.[4 19 23] However, combined inhibition produced by the VSCC blockers used was in excess of 100% (e.g. for norepinephrine release, nifedipine inhibited by 20%, ω-conotoxin GVI$_A$ by 35% and ω-agatoxin IV$_A$ by 88%; the combined inhibition was 143%) and ω-conotoxin MVII$_C$ inhibited norepinephrine and dopamine release completely at 1 µM. Therefore, these toxins at high concentrations produce less selective inhibition of VSCCs. This is in agreement with previous observations.[4 19]

A unifying target site for anaesthetic action remains elusive. However, the GABA$_A$ receptor represents an important target with which all anaesthetic agents so far examined (excepting ketamine, nitrous oxide and xenon) interact. Anaesthetic agents potentiate the GABA-induced chloride conductance, leading to hyperpolarization and depressed neurotransmission.[9–11]

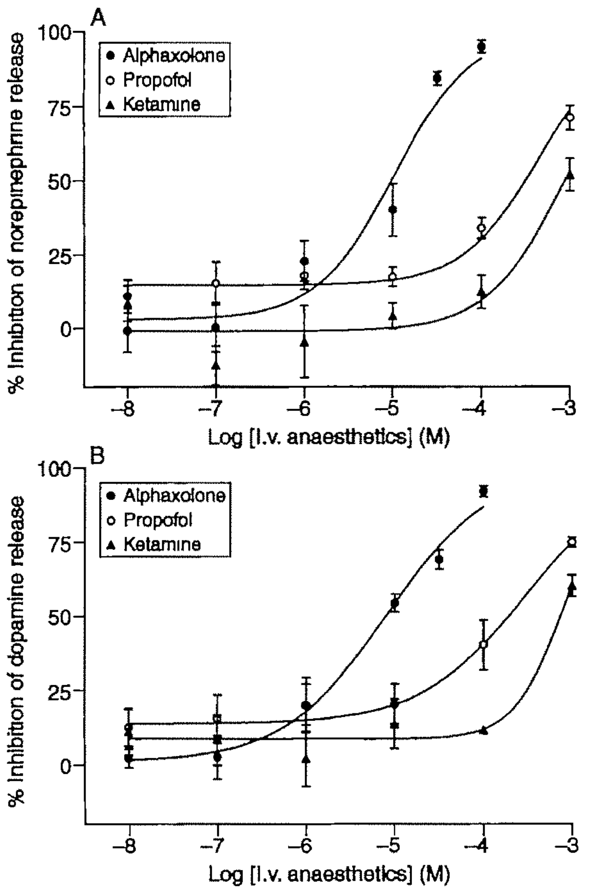

Fig 3 Effects of I.V. anaesthetics (alphaxalone, ketamine and propofol) on K$^+$-evoked release of norepinephrine (A) and dopamine (B). Data are mean and SEM (n=5 or 6).

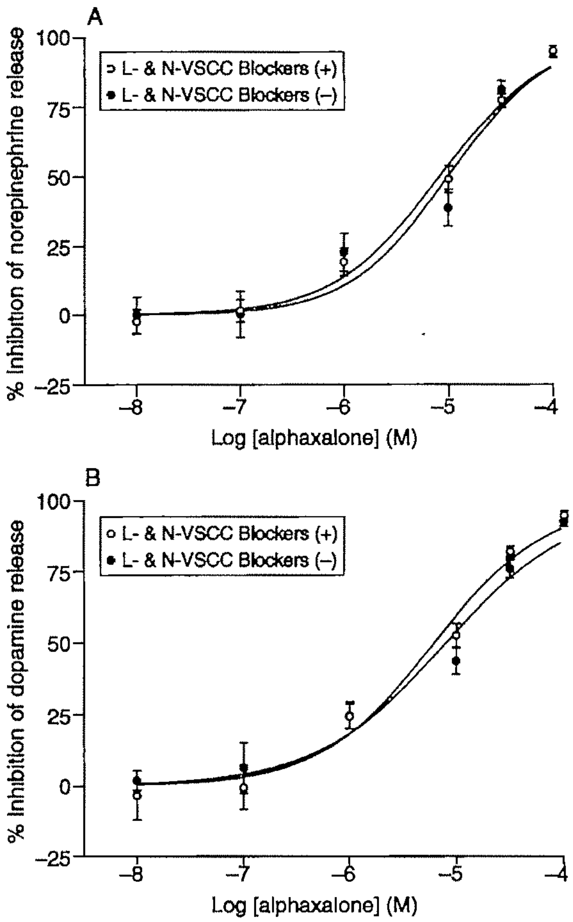

Fig 4 Concentration–response curves for alphaxalone inhibition of K$^+$-evoked release of norepinephrine (A) and dopamine (B) in the presence and absence of L- and N-type Ca^{2+} channel blockers Data are mean and SEM (n=6)

Table 3 pIC$_{25}$ and pIC$_{50}$ (mean IC$_{25}$ and IC$_{50}$) of i v. anaesthetics for K$^+$-evoked norepinephrine and dopamine release. Data are mean (SEM) *Plasma concentration of anaesthetic agent during anaesthesia (µM)

		I.v. anaesthetic agent		
	Catecholamine	**Alphaxalone**	**Propofol**	**Ketamine**
pIC$_{25}$ (mean IC$_{25}$)	Norepinephrine	5.68 (0.31)(2.1)	4.40 (0.07)(39.4)	3.63 (0.07)(232.0)
	Dopamine	5.53 (1.08)(2.9)	4.51 (0.12)(31.0)	3.62 (0.05)(239.3)
pIC$_{50}$ (mean IC$_{50}$)	Norepinephrine	5.11 (0.13)(7.8)	3.93 (0.07)(118.0)	3.16 (0.08)(700.2)
	Dopamine	5.14 (0.11)(7.2)	4.03 (0.12)(93.7)	3.14 (0.05)(720.1)
Clinical anaesthetic concentration*		7.5[14]	28[25]	9.2[25]

There is evidence to support a role for VSCCs as an additional cellular target for anaesthetic agents.[14,15] L-VSCC blockers such as verapamil and nitrendipine augment general anaesthetic potencies in laboratory animals.[24,26] We have also shown that i.v. anaesthetic agents (except ketamine) inhibit the binding of DHPs to L-VSCC, and there is a significant correlation between K_{25} and K_{50} for inhibition of DHP binding by anaesthetics and the peak plasma concentrations seen during anaesthesia.[16] In addition, several reports have show that clinically relevant concentrations of general anaesthetics inhibit DHP-insensitive Ca^{2+} currents.[27–29] However, we have recently questioned the role of this channel in man.[30]

A range of anaesthetic agents have been reported to inhibit excitatory synaptic transmission, and this may be via block of entry through receptor-operated and/or voltage-sensitive Ca^{2+} channels.[14] However, we have recently reported that propofol and thiopental inhibit glutamate release from rat cerebrocortical slices in a bicuculline-sensitive fashion, indicating that these anaesthetics are inhibiting release via an action at GABA receptors [31]. This inhibition may lead to some components of general anaesthesia, such as loss of consciousness and analgesia.

In the present study, alphaxalone produced concentration-dependent inhibition of norepinephrine and dopamine release, with IC_{25} and IC_{50} values occurring at clinically achievable concentrations.[14] In addition, propofol also produced concentration-dependent inhibition of norepinephrine and dopamine release, with IC_{25} values approaching those achieved clinically.[16] We have previously argued in favour of the use of IC_{25} for Ca^{2+} responses,[14,16] as relatively small increases in intracellular Ca^{2+} are capable of eliciting release. Although the total plasma concentration would be markedly reduced by protein binding, it should be noted that propofol is concentrated some eight-fold in the rat brain.[32] We therefore suggest that neuronal VSCCs represent an additional target for the action of alphaxalone and possibly propofol. The effects of ketamine observed in this study occurred at concentrations in excess of those encountered clinically,[33] and we therefore feel that the actions of this atypical anaesthetic[34] do not involve VSCCs. Moreover, it is well known that this anaesthetic agent acts at the NMDA–glutamate receptor.[13]

As the action of alphaxalone occurred in the clinically relevant range, we investigated this agent further. There were no significant differences in the IC_{50} values of alphaxalone for K^+-evoked norepinephrine and dopamine release in the presence and absence of nifedipine and ω-conotoxin GVI_A. These findings suggest that the inhibition by alphaxalone of norepinephrine and dopamine release may not be via the L/N-VSCC, implicating P/Q-type channels. However, Kameyama and colleagues[35] reported differential effects of isoflurane on VSCCs of the L, N and P/Q types, as the levels of inhibition of these channel currents produced by 0.5 mM isoflurane were 60, 35 and 15% respectively. This discrepancy may be a result of differences in the type of anaesthetic agent (steroid *vs* volatile anaesthetic), as alphaxalone and isoflurane produce different clinical anaesthetic effects. In addition, there are quantitative differences between electrically evoked and K^+-evoked neurotransmitter release.[22]

In summary, the present study shows that clinically achievable concentrations of alphaxalone significantly inhibit K^+-evoked norepinephrine and dopamine release from rat striatal slices, and this may be mediated by P/Q-type VSCCs. However, further studies examining bicuculline sensitivity need to be performed to determine any contribution of $GABA_A$ receptor activation to these responses.

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Spinal and supraspinal midazolam potentiates antinociceptive effects of isoflurane

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The effects of lumbar intrathecal (i.t.) and intracerebroventricular (i.c.v.) midazolam on nociception during isoflurane anaesthesia were studied in rats using the tail-flick test. Rats received i.t. midazolam 2 and 4 µg or i.c.v. midazolam 4 and 8 µg during 1.1, 1.2 and 1.3% isoflurane or without isoflurane. Neither i.t. nor i.c.v. midazolam alone at doses studied influenced nociceptive responses. 1.1% isoflurane showed a minimum antinociceptive effect which was not influenced by i.t. or i.c.v. midazolam. 1.2 and 1.3% isoflurane produced moderate antinociception which was markedly potentiated by both i.t. and i.c.v. midazolam. The effects of midazolam shown in the present study are different from the reported effects of midazolam on opioid-induced antinociception; where spinally administered midazolam potentiates and supraspinal midazolam inhibits the antinociceptive effects of morphine. The present results suggest that midazolam potentiates isoflurane-induced antinociception at doses where no effect is seen alone.

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Keywords: hypnotics benzodiazepine, midazolam; anaesthetics volatile, isoflurane; brain; spinal cord; rat

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Midazolam is commonly used as an adjunct to general anaesthesia and has been shown to decrease the anaesthetic requirements of volatile agents after i.v. administration in both animals[1] and humans.[2 3] However, in respect of a nociceptive action, both hyperalgesic[4 5] and antinociceptive[6] effects of systemically administered midazolam have been reported. Different results may be ascribed to the action of midazolam on the spinal cord and/or brain. Regionally administered midazolam within the central nervous system has been reported to produce different effects on nociception. Lumbar intrathecal (i.t.) administration of midazolam produces antinociception,[4 7 8] while intracerebroventricular (i.c.v.) injection produces a hyperalgesic response.[5] In combination with opioids, the effects of midazolam on nociception are also different depending on the route of administration; where i.t. injection potentiates the antinociceptive effects of morphine and i.c.v. injection inhibits opioid-induced antinociception.[9–11] These modulating effects of midazolam on opioid-induced antinociception have been suggested to be mediated at least partially through gamma-aminobutyric acid $_A$ (GABA$_A$) receptors.[9 10 12] With respect to the interaction of i.t. midazolam with inhalation anaesthetics, there has been one report[13] which showed that i.t. midazolam decreased isoflurane minimum alveolar concentration (MAC) in rats. No study has examined whether a difference exists between the spinal and supraspinal actions of midazolam on antinociception induced by a volatile anaesthetic as observed in narcotic-induced antinociception. The current study therefore examined the influence of i.t. or i.c.v. midazolam on nociception in rats anaesthetized with various concentrations of isoflurane.

Materials and methods

This study was approved by the Committee of Ethics on Animal Experiments at the Yamaguchi University School of Medicine.

Male Wistar rats weighing 250–300 g (60–70 days after birth) were used. The animals were housed in a cage at 21–25 °C under diurnal light condition and allowed free access to food and water prior to the experiment.

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For implantation of an i.t. catheter, rats were anaesthetized with halothane, and a PE-10 catheter was aseptically inserted through the atlanto-occipital membrane into the intrathecal space. The catheter was advanced 8 cm caudally to position its tip at the level of lumbar enlargement of the spinal cord and secured to the subcutaneous tissue.

For implantation of an i.c.v. cannula, rats were anaesthetized by intraperitoneal administration of pentobarbital (50 mg kg^{-1}) and a 24-G stainless steel cannula was stereotaxically inserted into the right lateral ventricle under aseptic conditions according to the atlas of Paxinos and Watson (1986) (0.8 mm posterior from bregma, 1.5 mm lateral from the midline and 3.5 mm depth from the skull). The cannula was fixed to the skull bones with methyl methacrylate cement.

A minimum period of 48 h elapsed between catheter implantation and the following experiment which was performed in animals with no neurobehavioural abnormality.

All catheters' positions were verified at the end of experiment; i.t. catheter-implanted rats were given i.t. injection of 10 μl of 2% lidocaine and all showed bilateral paralysis hindlimbs. In addition, for postmortem confirmation, i.t. catheter position and i.c.v. cannula, and for the assessment of the spread of solution, 10 μl and 5 μl of Evans Blue was injected i.t. and i.c.v., respectively.

Rats implanted with either i.t. catheter or i.c.v. cannula were assigned into four groups; Group I (*n*=24) received no inhalation of isoflurane, Groups II, III and IV (*n*=30 in each) received isoflurane 1.1%, 1.2% and 1.3%, respectively. Group I was further divided into four midazolam-treated groups (*n*=6 in each), each of which received 2 μg i.t., 4 μg i.t., 4 μg i.c.v. and 8 μg i.c.v. Each of Groups II, III and IV was further divided into five groups (*n*=6 in each): control group that received either i.t. (*n*=3) or i.c.v. (*n*=3) saline and four midazolam groups (2 μg i.t., 4 μg i.t., 4 μg i.c.v. and 8 μg i.c.v.).

Midazolam (F. Hoffmann-La Roche, Swiss) was dissolved in 0.9% saline, so that desired dose was contained in 10 μl for i.t. injection or 5 μl for i.c.v. injection. In control groups at each isoflurane concentration, rats received 10 μl of i.t. saline or 5 μl of i.c.v. saline. The i.t. and i.c.v. injections were made using a microsyringe over a period of 5 min and 10 min, respectively.

The doses of midazolam and concentrations of isoflurane were selected on the basis of our preliminary results and of reported information.[11–13] Preliminarily, using rats with femoral artery catheterization, we found that Pa_{CO_2} and mean arterial pressure respectively were maintained at 4.7–6.0 kPa and above 70 mm Hg for more than 120 min under spontaneous respiration at 1.3% isoflurane alone or with i.c.v. administration of 8 μg midazolam. Rats given midazolam 4 μg i.t. or 8 μg i.c.v. behaved normally. When the isoflurane concentration was increased to 1.4%, tail-flick latencies were prolonged to greater than 15 s and severe respiratory depression or sometimes death ensued.

Before administration of midazolam or isoflurane, an awake value of tail-flick latency (Analgesia meter, MK-330, Muromachi Kikai, Tokyo) was measured in each rat. The tail of each rat was placed on a focused projector lamp so that the beam was focused on the proximal third of the tail. The end-point of the test was represented by the number of seconds until the rat removed its tail from the beam. Beam intensity was regulated so that pre-anaesthetic awake latencies were 4–5 s. The cut-off time was set at 15 s.

Rats of Group I were minimally restrained in a specially designed plastic box flushed continuously with total 2 litres min^{-1} of nitrogen and oxygen (FI_{O_2}=0.25). In the other groups, anaesthesia was induced with 3% isoflurane in the same gas mixture as Group I (FI_{O_2}=0.25) and, thereafter, maintained with preselected anaesthetic concentrations (1.1%, 1.2% and 1.3%) under spontaneous respiration until the end of experiment. The concentrations of inhalational isoflurane and oxygen were monitored continuously with a Datex Capnomac Anesthetic monitor (Helsinki, Finland). Rectal and skin temperature of the tail base were measured by a digital thermometer (6510 TC, Mallinckrodt Medical Inc., Ireland). Application of thermister probe neither disturbed spontaneous movement of the tail nor influenced tail-flick latencies. Rectal and tail temperatures were maintained by means of external heating at 36.8–37.2°C and 36.2–36.4°C, respectively.

After a 30-min stabilization period at each concentration of isoflurane (Groups II–IV), baseline tail-flick latencies were measured, and then midazolam or saline was administered i.t. or i.c.v. In order to avoid repeated stimulation without anaesthesia, the baseline measurement was omitted in Group I, and midazolam was administered i.t. or i.c.v. after a 30-min stabilization.

Measurement of tail-flick latencies were repeated at 10, 15, 20, 30, 45, 60, 90 and 120 min after the administration of midazolam or saline.

The antinociceptive effects of isoflurane and midazolam were expressed as percentage of the maximum possible effect (% MPE) as follows:

$$\% \text{ MPE}=(\text{postdrug value} - \text{awake value})/(\text{cut-off time} - \text{awake value})\times 100.$$

Analysis of variance for repeated measures was used to evaluate the time-course effect of treatments. To compare % MPE and maximum antinociceptive effect (peak % MPE) among groups, factorial analysis of variance was used. Multiple comparisons were performed using Fisher's protected least significant difference test. $P<0.05$ was considered statistically significant.

Results

In Group I (isoflurane 0%), i.t. or i.c.v. midazolam alone studied did not significantly change % MPE over the 120-min observation period.

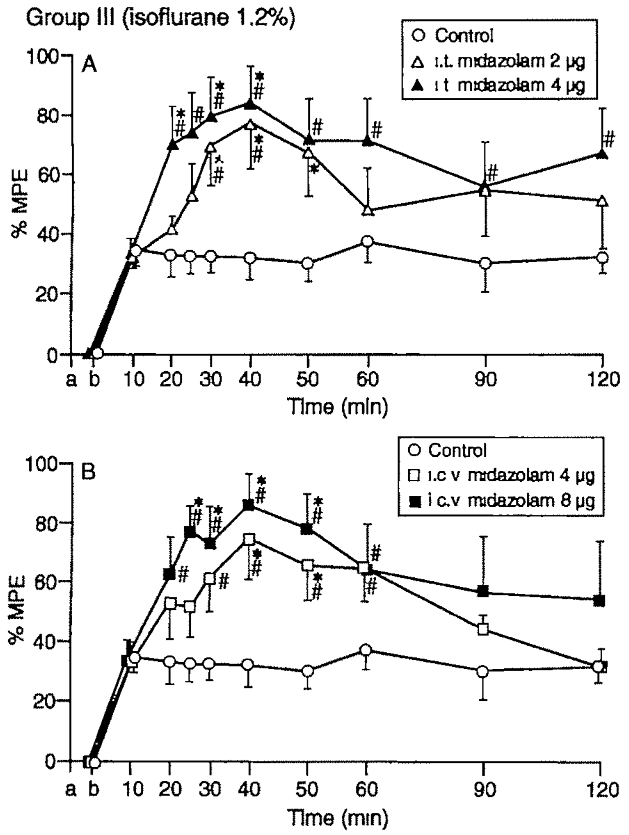

Fig 1 Time course of antinociceptive effects (% MPE) of intrathecal (A) and intracerebroventricular (B) administration of saline or midazolam during 1.2% isoflurane. Data are mean (SEM). a=awake values before inhalation of isoflurane, b=baseline values at 1.2% isoflurane before administration of saline or midazolam, i.t.=intrathecal, i.c.v.=intracerebroventricular. In the control group given saline, isoflurane 1.2% increased % MPE significantly ($P<0.05$) compared with the awake value (a) and the significant elevation continued for 120-min period after saline injection under the isoflurane anaesthesia. *$P<0.05$ *vs* control group, #$P<0.05$ *vs* baseline value (b) of the group.

In the control group at each concentration of isoflurane (Groups II, III and IV), there were no differences in % MPE between i.t. and i.c.v. saline administration and therefore the data of i.t. and i.c.v. saline at each isoflurane concentration were combined and served as control.

In Group II, mean % MPE of the control group was significantly but minimally increased to 6–10% during 1.1% isoflurane when compared with the awake value. Neither i.t. nor i.c.v. midazolam caused further changes in % MPE following administration.

The time courses of % MPE after administration of i.t. and i.c.v. midazolam in Groups III and IV respectively are shown in Figures 1 and 2. In Groups III and IV, mean % MPE of the control group was significantly increased to 31–38% during 1.2% isoflurane and to 45–51% during 1.3% isoflurane when compared with awake values. Both i.t. and i.c.v. midazolam at all doses caused a further increase in % MPE (Figs 1, 2). At each anaesthetic concentration, there were no significant differences in % MPE between midazolam given either i.t. or i.c.v.

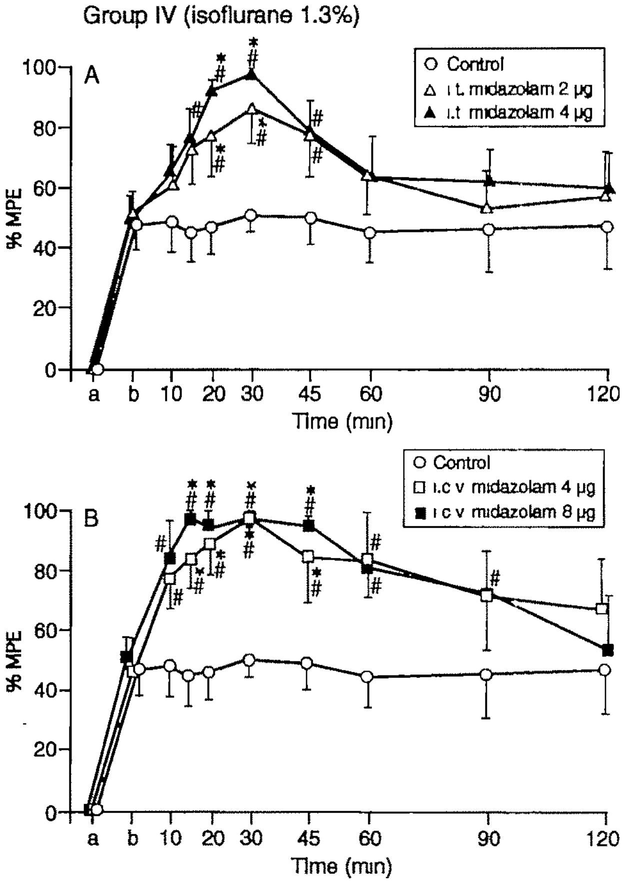

Fig 2 Time course of antinociceptive effects (% MPE) of intrathecal (A) and intracerebroventricular (B) administration of saline or midazolam during 1.3% isoflurane. Data are mean (SEM). a=awake values before inhalation of isoflurane, b=baseline values at 1.3% isoflurane before administration of saline or midazolam, i.t.=intrathecal, i.c.v.=intracerebroventricular. In the control group given saline, isoflurane 1.3% increased % MPE significantly ($P<0.05$) compared with the awake value (a) and the significant elevation continued for 120-min period after saline injection under the isoflurane anaesthesia. * $P<0.05$ *vs* control group, # $P<0.05$ *vs* baseline value (b) of the group.

Table 1 shows peak % MPE (maximum % MPE during the measurement period in each rat) in each group. In Group I (isoflurane 0%), there were no differences in peak % MPE between the subgroups given i.t. or i.c.v. midazolam. In Group II (1.1% isoflurane), there were no significant differences in peak % MPE between control and any treatment groups given midazolam. In Groups III and IV (1.2 and 1.3% isoflurane), there were significant differences in peak % MPE between respective control and all treatment groups with no inter-treatment group differences. Peak % MPEs in control and all treatment subgroups in Groups III and IV are significantly higher than those in the corresponding subgroups of Groups I and II. There were no differences in peak % MPE in any subgroup between Groups III and IV, and no difference between Groups I and II.

Postmortem examination revealed that Evans Blue injected through the i.t. catheter and i.c.v. cannula spread

Table 1 I.t. and i.c.v. midazolam potentiated antinociceptive effects of isoflurane. Peak % MPE (mean (SEM)) in each group inhaled isoflurane concentration. Peak % MPE is a peak value of % MPE of the rat during the experiment. i.t.=intrathecal administration, i.c.v.=intracerebroventricular administration. *$P<0.005$ compared with the control group at the corresponding concentration of isoflurane. †$P<0.025$ compared with the corresponding subgroup of Group I. ‡$P<0.005$ compared with the corresponding subgroup of Group II

		Midazolam			
	Control	**2 µg i.t.**	**4 µg i.t.**	**4 µg i.c.v.**	**8 µg i.c.v.**
Group I 0%		3.9 (1.6)	6.3 (1.4)	6.0 (1.3)	5.3 (2.7)
Group II 1.1%	13.6 (3.1)	16.3 (2.7)	19.1 (7.8)	16.3 (2.0)	14.4 (2.5)
Group III 1.2%	48.2 (7.0)‡	90.3 (9.7)*†‡	83.7 (11.9)*†‡	90.2 (9.0)*†‡	92.5 (7.5)*†‡
Group IV 1.3%	63.2 (9.8)‡	90.4 (7.1)*†‡	97.7 (1.5)*†‡	100 (0)*†‡	100 (0)*†‡

in the lumbar spinal cord and in both lateral cerebroventricles and third ventricle, respectively.

Discussion

In the present study, isoflurane 1.1–1.3% showed antinociceptive effects in a dose-related fashion, and both spinal and supraspinal administration of midazolam at doses not affecting nociceptive responses alone potentiated the antinociception produced by isoflurane 1.2 and 1.3%. These results are in contrast to the reported effects of midazolam on opioid-induced antinociception which depend on the route of administration of midazolam (i.e., i.t. injection of midazolam potentiates opioid-induced analgesia, while i.c.v. injection inhibits).[9–11]

Anatomical localization of the spinally or supraspinally administered agents in addition to their effects on motor function deserve comment. We confirmed that the distribution of Evans Blue injected i.t. (10 µl) and i.c.v. (5 µl), was confined in the spinal and supraspinal localization, respectively. Thus, either effect of i.c.v. and i.t. drug is assumed independent, and not resulted from distribution to the remote subarachnoid space. As for the motor function, we did not observe any disturbance induced by midazolam at doses studied. Our i.t. doses of midazolam are far less than the minimum dose (40 µg) of i.t. midazolam required to produce catalepsy.[11] Midazolam 8 µg i.c.v. has been shown to cause catalepsy in rats.[11] However, in the present study, no animals exhibited catalepsy, and thus the observed results have not been influenced by motor disturbance.

Several studies have demonstrated that intravenous midazolam decreased the requirement for volatile anaesthetic agents.[1–3] However, little is known about the exact site or mechanism of action. There has been only one report to our knowledge investigating the interaction of i.t. midazolam with inhalation anaesthetics with respect to nociception or anaesthetic potency.[13] Schwieger and co-workers[13] reported in rats that i.t. midazolam decreased isoflurane MAC in a dose-dependent manner. A dose of 5 µg of i.t. midazolam decreased isoflurane MAC by 16%[13] which is comparable with our observations that i.t. injection of 2 and 4 µg of midazolam potentiated the antinociception produced by 1.2 and 1.3% isoflurane. I.t. injection of midazolam alone has been reported to produce antinociception in humans[14] and animals[7,9–11,15] which is believed to be mediated by potentiation of the effects of GABA on $GABA_A$ receptors. However, over the range of the doses studied (2–4 µg), no significant antinociceptive effects of i.t. midazolam have been reported in rats[11] as observed in the present experiments. Several studies have indicated that the spinal cord is an important site for antinociceptive action of inhalation anaesthetics,[16–19] as assessed by a blockade of motor response to noxious stimulation. Mason, Owens and Hammond[20] have shown that suppression of pinch-evoked movement by halothane is antagonized by i.t. injection of bicuculline and picrotoxin at doses that have no influence on the response latency when given alone, suggesting that halothane exerts its antinocifensive action through a $GABA_A$ receptor-related mechanism within the spinal cord.

The potentiating effect of i.t. midazolam on antinociception induced by isoflurane in the current study is likely to be mediated by enhancement of the action of GABA on $GABA_A$ receptor in the spinal cord. Furthermore, antinociceptive effects of i.t. midazolam is suggested to be mediated via mechanisms related to opioid receptors.[7,15,21] Goodchild and co-workers[8] have strongly suggested that i.t. midazolam causes antinociception by a mechanism involving the delta opioid receptor. This possibility, though not examined in the present study, may be in part responsible for the observed potentiation.

In contrast to the observation that opioid-induced antinociception was antagonized by i.c.v. midazolam, i.c.v. injection of midazolam potentiated isoflurane-induced antinociception in the present study. The potentiating effects of isoflurane-induced antinociception by i.c.v. midazolam might be attributable to anaesthetic efficacy in contrast to analgesic effects of midazolam. However, such speculation cannot readily explain the current results. I.c.v. midazolam, given with 1.1% isoflurane, produced no potentiation, while the effect of 1.2 and 1.3% isoflurane (baseline % MPE: 35–50%) were increased by i.c.v. midazolam (% MPE to 90–100%). Although the possibility that an undetectable anaesthetic efficacy of midazolam may have contributed to increase the antinociceptive effects induced by isoflurane 1.2 and 1.3% cannot be entirely excluded, the fact that there was no modulatory effect of the same doses of midazolam given with isoflurane 1.1% suggests this possibility is unlikely.

Several investigators have recently demonstrated that anaesthetic potency measured as MAC is determined by the action of anaesthetics at the spinal cord and/or brain stem. Isoflurane MAC for goats was increased during preferential delivery of isoflurane to the brain and decreased during preferential delivery to the spinal cord, compared to MAC measured by systemic administration.[16 17] Rampil[19] also showed that MAC was not changed after spinal cord transection in rats. The results of these studies suggest that deepening of anaesthetic level by i.c.v. midazolam (even if this occurs) may not obscure the somatic response to the stimulation.

Anaesthetic potency of an agent does not necessarily correlate with analgesic action. Deady and co-workers[22] found that the ratio of anaesthetic potency measured by MAC or concentration inhibiting righting reflex *versus* analgesic potency measured by tail-flick latency was different among volatile anaesthetics. Niv and co-workers[4] also reported in rats that intraperitoneal injection of 10 mg kg^{-1} of midazolam produced complete abolition of spontaneous movement but decreased tail-flick latencies compared with the awake values, suggesting a dissociation between anaesthetic depth and analgesic actions.

With respect to i.c.v. administration of midazolam alone, our results are consistent with a previous report which observed only minor influence, if any, on nociceptive responses.[11] In addition to enhancement of the binding of GABA to $GABA_A$ receptors, midazolam has been reported to inhibit GABA metabolism in brain synaptosomes, suggesting GABA concentrations may be increased at the synapse.[23] Volatile anaesthetics also have modulatory actions on the function of $GABA_A$-mediated inhibitory systems in the brain. This modulation seems to contribute to anaesthetic and possibly analgesic action, though the modulatory effects of anaesthetics are not simple. Banks and Pearce[24] reported that volatile anaesthetics produced both reduction of the peak amplitude and prolongation of the duration of miniature inhibitory postsynaptic currents in hippocampal neurons of brain slices, and concluded that net action is via enhanced inhibition. Moreover, in an *in vitro* study it was suggested that isoflurane also increases GABA levels in the synaptic cleft and thus may enhance synaptic inhibition.[25] When used in conjuction with opioids, i.c.v. injection of midazolam has been shown to inhibit the antinociceptive effects of opioids through a mechanism related with $GABA_A$ receptor.[9 10 12] In addition, Rady and Fujimoto[9] have demonstrated an elimination of the effect of i.c.v. midazolam by i.t. pretreatment with dynorphin antiserum, indicating that the inhibitory effect of i.c.v. midazolam on opioid antinociception is mediated by the release of dynorphin A (1–17) in the spinal cord. Dynorphin A (1–17) is a putative endogenous kappa selective opioid and is reported to be a mediator of antianalgesic descending system in the spinal cord.[26] To our knowledge, the effects of volatile anaesthetics on antianalgesic descending systems have not been investigated. It has been reported that isoflurane dose-dependently blocks spinal cord potentials evoked by a feedback loop through supraspinal structures,[27] though the relationship relevance to our data is unclear. When considering the effects of volatile anaesthetics on opioid receptor subtypes, various results have been reported. Campbell, Rowbotham and Lambert[28] reported that clinical concentrations of halothane had little effect on mu and delta opioid receptor binding, whereas in another study halothane inhibited both mu and kappa receptor binding.[29] These modulating effects of volatile anaesthetics and midazolam on $GABA_A$ and/or opioid receptors in the brain may contribute the potentiating effects of i.c.v. midazolam on isoflurane-induced antinociception in the current study, though the precise mechanism remains to be elucidated.

In summary, both spinal and supraspinal midazolam at doses with no antinociceptive effects alone, potentiated isoflurane-induced antinociception. These results are different from the effects of midazolam on opioid-induced antinociception, which is potentiated by spinal administration but inhibited by supraspinal injection of midazolam. The present study suggests that low doses of midazolam may enhance the antinociceptive effects of isoflurane.

Acknowledgements

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BJA

REVIEW ARTICLE

Production of human albumin solution: a continually developing colloid

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Keywords: blood, replacement; protein, albumin

Albumin has a long history of clinical use in colloid replacement therapy dating back over 50 yr. It is currently used in greater volume than any other biopharmaceutical solution that is available, and worldwide manufacturing is of the order of 100s of tonnes annually. However, as with many therapies, the clinical use of albumin has often had its critics. Some of these[6] have concluded that albumin therapy may carry an increased risk of death, relative to crystalloid solutions, in some critical care situations.

When assessing the place for albumin in critical care therapy, the nature of the product being infused should be considered. Less pure preparations, such as plasma protein fraction, have been replaced by purer preparations with lower associated adverse reactions. Many of the earlier studies of albumin use were conducted in the 1970s and 1980s. Since that time, human albumin solution has been refined by developments and improvements to manufacturing processes, so that modern albumin is far removed from the solutions infused in earlier decades.

Albumin solution for therapy should be as near as possible to the native protein found in the plasma, given the need for purification and viral assurance. This review outlines key changes in the production of albumin for clinical use, focusing in particular on the substantial improvements in purity and tolerability that have been achieved in the last 20 yr. It also provides an up-to-date profile of a continually improving product.

Properties and clinical use of albumin

Albumin is a highly water-soluble protein (molecular weight 66 000 Da) with considerable structural stability. It is an important component of plasma, making up 60% of the total protein. At normal physiological concentrations of plasma proteins, albumin contributes 80% of the colloidal osmotic (oncotic) pressure of the plasma, and its function as a carrier for hormones, enzymes, fatty acids, metal ions and medicinal products is much reported.[32]

Human albumin has been used as a therapeutic agent for over 50 yr. Its key indication is the restoration and maintenance of circulating blood volume in situations such as trauma, surgery and blood loss, burns management and plasma exchange.[26] The ideal product for this purpose would be monomeric albumin of very high purity. free from contamination with other plasma proteins, endotoxins, metal ions, albumin aggregates and prekallikrein activator (PKA), as such impurities appear to influence the tolerability of albumin infusion.[11]

Experience with albumin products of the older generation suggests that high endotoxin concentrations may be implicated in febrile reactions, while high concentrations of PKA can cause hypotension.[2] Aluminium concentrations need to be kept very low to avoid accumulation in neonates and patients with impaired renal function.[23] Contamination with trace proteins may result in undesirable aggregation when albumin is being pasteurized.[18] The goal for manufacturers in recent decades has therefore been to minimize or eliminate such impurities.

Virus safety

The safety record of albumin products with respect to virus transmission over the past 50 yr has been excellent. Pasteurization at 60°C for 10 h was introduced in the 1940s[13 14] and has been shown to inactivate a range of lipid-enveloped and non-enveloped viruses,[27] including hepatitis A, B and C and HIV. The inclusion of stabilizers ensures that the albumin solution is not denatured on heating. Pasteurization in the final container after filling removes the potential for late contamination.

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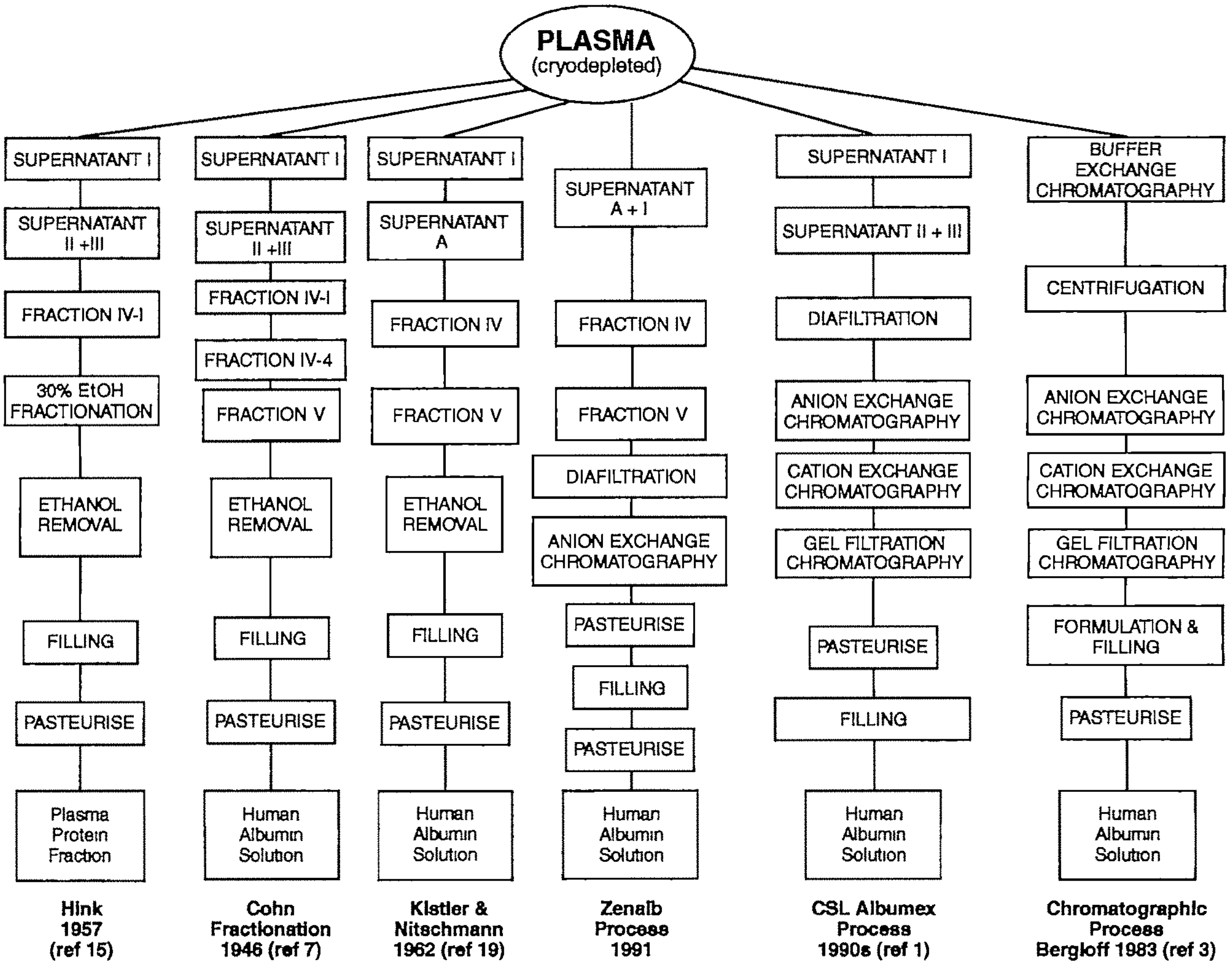

Fig 1 Schematic flow diagram comparing traditional methods for the preparation of plasma protein fraction and human albumin solution[1 7 15 19] with modern processes which incorporate chromatography (Zenalb® BPL and Albumex CSL) and those which are wholly chromatographic (Bergloff). Details of the processes are given in the references cited beneath each process

Methods of preparation

Albumin is now predominantly derived from human plasma, although both time-expired blood and, in some countries, placental material have been used as sources in the past. The rise in the use of packed red cells rather than whole blood transfusions means that the amount of albumin derived from time-expired blood has declined markedly, while the use of placental material was abandoned because of difficulties in ensuring donor traceability, particularly in terms of viral status.

Albumin products fall into two categories. The plasma protein fraction (PPF)[15] is broadly similar to human albumin solution (HAS) and is derived (Fig. 1) by a higher-yielding process but has a lower minimum albumin purity (>85% for PPF *vs* ≥95% for HAS). Its main disadvantage is the presence of hypotensive contaminants, particularly PKA.[20 30] Consequently, and with greater supplies of plasma becoming available, PPF has fallen in popularity and is no longer listed in the British Pharmacopoeia. Some PPF products are still available outside the UK.

The traditional method for the purification of albumin for therapeutic use has been cold ethanol fractionation, as described by Cohn and colleagues in 1946[7] and its later variants. Since then, some pharmaceutical providers have chosen to supplement this process with additional purification steps[1] while others have moved towards an alternative, predominantly chromatographic separation method.[40] A schematic representation of the different processes is shown in Fig. 1.

Cold ethanol fractionation

Albumin has some unique properties that allow relatively simple and effective purification by precipitation methods. It has the highest solubility and the lowest isoelectric point (the pH at which it bears no net charge) of the major plasma proteins. Adjustments to pH, temperature, ionic strength,

Table 1 Comparison of changes in some of the pharmacopoeial requirements for human albumin over the period 1988–1999 Information derived from the relevant year's pharmacopoeia. IEP = immunoelectrophoresis

Criterion	**BP 1988** **Plasma protein fraction**	**BP 1988** **Human albumin solution**	**BP 1993** **Human albumin solution**	**BP 1999** **Human albumin solution**	**EP 1997** **Human albumin solution**
Source material	Plasma/serum	Plasma/serum/placenta	No change	Plasma	No change
Albumin purity	≥85%	≥95%	No change	No change	No change
Albumin concentration	4–5%	15–25%	No change	No change	No change
		4–5%	No change	3.5–5%	No change
Stabilizer	Octanoate	Octanoate	Octanoate	Octanoate and/or *N*-acetyl tryptophan	Octanoate and/or *N*-acetyl tryptophan
Sterility	Passes text	No change	No change	No change	No change
Antimicrobial agent	None	No change	No change	No change	No change
Pasteurization	10 h at 60°C	10 h 60 ± 0.5°C	No change	No change	≥10 h at 60 ± 0.5°C
Sterility check 30–32°C	Incubate ≥14 days	No change	No change	No change	No change
Sterility check 20–25°C	Incubate ≥4 weeks	No change	No change	No change	No change
Appearance	Clear pale yellow liquid	Almost colourless or amber	No change	Almost colourless, yellow or green	No change
Human identity (using specific antisera)	Precipitation/IEP Electrophoretic profile distinct from HAS	Precipitation/IEP Electrophoretic profile distinct from PPF	Precipitation/IEP Electrophoretic profile distinct from PPF	Precipitation/IEP	Precipitation/IEP
pH	6.7–7.3	No change	No change	No change	No change
Alkaline phosphatase activity (u g^{-1})	≤0.1	No change	No change	Not required	No change
Haem content: absorbance at 403 nm, 1% solution	≤0.15	No change	No change	No change	No change
Prekallikrein activator	Not defined	No change	No change	≤35 iu ml^{-1}	No change
Aggregates	Unretained peak ≤10% of total nitrogen content run on dextran gel	Unretained peak ≤5% of total nitrogen content run on dextran gel	No change	Aggregate peak area/2 ≤5% (HPLC)	No change
Potassium (μmol g^{-1})	≤50	No change	No change	No change	No change
Sodium (mmol $litre^{-1}$)	≤160	No change	No change	No change	No change
Abnormal toxicity	Pass	No change	No change	Not required	No change
Storage in dark	5 years 2–8°C, 3 years ≤25°C	No change	No change No change	No timescales given	No change
Aluminium (μmol $litre^{-1}$)	Not defined	No change	≤200 if for use in premature infants or for dialysis	No change	No change
Indication of suitability for dialysis and in premature infants	Not stated	Not stated	Stated on label	No change	No change
Origin of albumin	Not stated	Stated on label	No change	No change	Not stated
Pyrogenicity	Test in rabbits, dose 3 ml kg^{-1} body weight	Test in rabbits; dose 3 ml kg^{-1} body weight	Test in rabbits; dose 3 ml kg^{-1} body weight	Test in rabbits; dose 10 ml kg^{-1} (5% product), 3 ml kg^{-1} (20% product)	No change

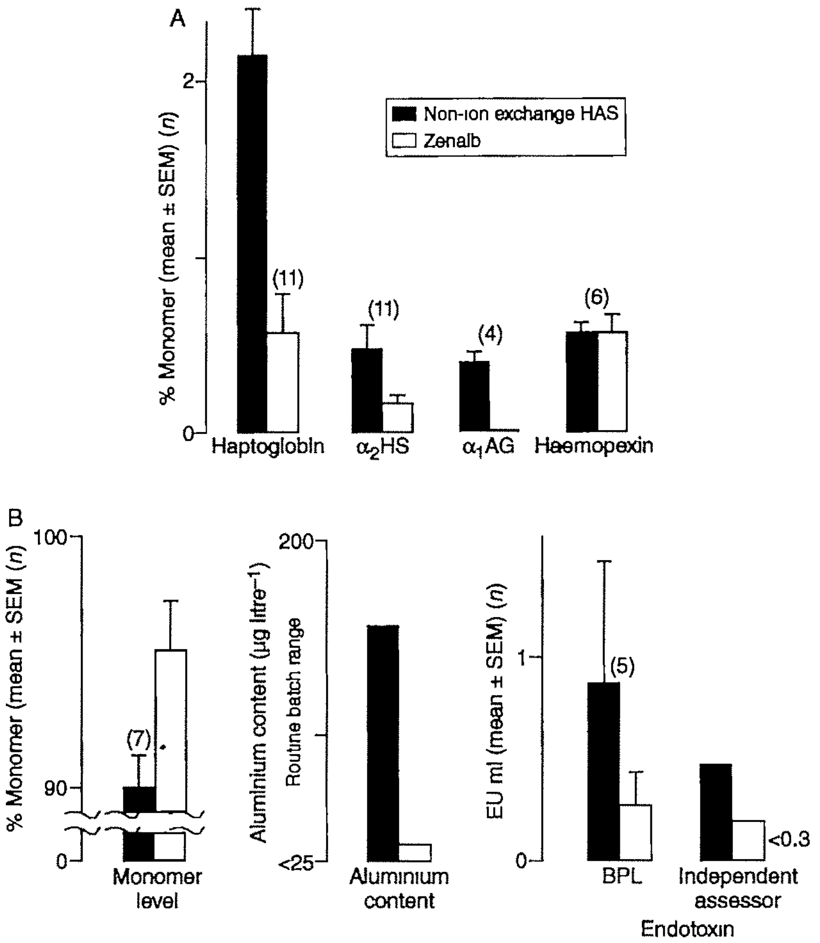

Fig 2 (A) Comparisons of previous BPL human albumin solution and the Zenalb® product Concentrations of four common plasma protein impurities measured by radial immunodiffusion for the laboratory-scale process. α_2-HS = α_2-HS glycoprotein; α_1-AG = α_1-acid glycoprotein. (B) Some properties of albumin produced at production/pilot batches for previous BPL human albumin solution and Zenalb® Monomer content was measured by FPLC (Pharmacia) size exclusion chromatography, aluminium content by atomic absorption spectrometry and endotoxin concentrations by the *Limulus* amoebocyte lysate assay

ethanol concentration and protein concentration therefore allow the separation of albumin from the other plasma proteins. Seventeen disulphide bonds along the single polypeptide chain confer considerable structural stability, so that under conditions in which other valuable plasma proteins would be totally denatured, albumin is recovered relatively undamaged.

There are two cold ethanol fractionation processes in common use; these are compared in detail elsewhere.[28] Many American suppliers have retained the original Cohn process.[7] The Kistler and Nitschmann process, which uses fewer protein precipitation steps and hence less ethanol, is more cost-effective,[19] and has been favoured by some European fractionators (Fig. 1). The valuable coagulation factors are removed as cryoprecipitate on initial thawing of the plasma before cold ethanol fractionation. With either method, an initial low ethanol precipitation stage removes the fibrinogen from the source plasma. Subsequently, by raising the ethanol concentration to 25% at pH 6.9 for the Cohn method or 19% at pH 5.85 for the Kistler and Nitschmann method, the immunoglobulins are precipitated while the albumin remains in solution. Albumin is then isolated from the majority of the other plasma contaminants (mainly α and β globulins), which are precipitated by the further addition of ethanol to a final ethanol concentration of 40%. This is carried out in two stages in the Cohn process but as a single step in the Kistler and Nitschmann method. In a final step, the albumin is itself precipitated near its isoelectric point. The precipitate paste (fraction V) can be held frozen before further processing.

Chromatographic purification

An alternative to cold ethanol fractionation is the chromatographic purification of plasma to produce albumin. This method was first described in the early 1980s.[3 8 40] After clarification, the plasma is buffer-exchanged by either column gel filtration or diafiltration to allow subsequent ion exchange chromatography. There follows one or more

Table 2 Summary of spontaneous adverse reaction reports for human albumin solution (HAS) received by the BPL Medical Department (1993–1997) *Serious adverse reactions include fatal or life-threatening reactions, or cause persistent or significant disability/incapacity, or result in or prolong hospitalization, or lead to congenital anomalies or birth defects **One infusion estimated as 500 ml of 4·5% HAS or 100 ml of 20% HAS

Severity of adverse reactions	Body system	Human albumin solution 4.5%		Human albumin solution 20%	
		No. of symptoms	No. of patients	No. of symptoms	No. of patients
Non-serious*	Cardiac	9	8	0	0
	Dermatological	2	2	1	1
	Gastrointestinal	2	2	0	0
	General	23	11	1	1
	Musculoskeletal	1	1	0	0
	Neurological	4	3	0	0
	Respiratory	3	3	0	0
	Vascular	8	8	0	0
	Subtotal	52	17	2	1
Serious*	Cardiac	0	0	4	2
	Dermatological	1	1	0	0
	Gastrointestinal	3	2	0	0
	General	10	4	1	1
	Neurological	2	1	1	1
	Respiratory	0	0	7	4
	Vascular	2	2	2	1
	Subtotal	18	5	15	4
	Grand total	70	22	17	5
Total volume of albumin issued (litres)		602 000		133 000	
Approximate number of infusions**		1 204 000		1 330 000	
Total number of reported adverse reactions		70		17	
Incidence of adverse reactions per infusion		1.17 200		1·78 200	

column chromatographic purification steps, then further gel filtration chromatography or buffer exchange.

The appeal of chromatographic processing of plasma over cold ethanol fractionation in principle is its ease of automation, the relatively inexpensive plant required, and the ease of sanitizing and maintaining a Good Manufacturing Practice environment. The process is potentially less damaging to the protein than ethanol precipitation, and the concentration of aggregation resulting from processing is minimized. The yield of albumin is also generally higher by chromatographic methods (80–85% yield at >98% purity) than by cold ethanol precipitation (typically 60–70% yield and a 95% pure product).

Despite these potential advantages, chromatographic albumin purification has not been widely adopted until relatively recently because of the limited availability of the very large chromatographic equipment required to meet demand for the product.

Other methods

A combined method, whereby chromatographic purification steps supplement the cold ethanol fractionation process, has been adopted by a number of manufacturers. Single or multiple column steps can improve product purity by allowing convenient buffer exchange and depleting trace protein contaminants. Several other strategies for the purification of albumin have been evaluated over the past 50 yr but none has been adopted on a large scale. These are discussed more fully elsewhere.[28]

Pharmacopoeial standards for albumin products

Human albumin is produced at two concentrations. The 4–5% albumin solution is an isotonic solution particularly suitable for fluid replacement in hypovolaemia. The 20–25% albumin is a hypotonic but hyperoncotic solution for the treatment of fluid loss where electrolyte or fluid load is contraindicated. The highly concentrated protein solution provides colloidal pressure while minimizing the additional salts and fluid volume that are infused. These low-salt, high-concentration albumin products are also used to treat patients with poor renal function, to avoid electrolyte disturbances, and in the treatment of neonates. Electrolyte balance can be maintained more accurately by tailoring the use of appropriate crystalloids with the 20% albumin solution.

An examination of the changes to the pharmacopoeial requirements for albumin products over the past decade provides an interesting insight into alterations in processing methodologies and the resulting product improvements. Thus, a review of the requirements of the British Pharmacopoeia (BP) dated 1988, 1993 and 1999 and the European Pharmacopoeia (EP) 1997 (Table 1) shows the move away from allowing placental sources, and the introduction of maximal permitted concentrations for PKA and aluminium. Improvements in analytical technology are reflected in the use of HPLC (high-performance liquid chromatography) rather than soft gel chromatography for the measurement of aggregates. Screening of plasma pools for hepatitis C was introduced once the causative agent had been identified. Finally, the defined appearance of albumin solutions has been broadened to permit green coloration, as anion exchange-purified albumin generally has a green colour[25] resulting from the conversion of bound bilirubin to biliverdin by oxidation during the pasteurization step.

Developments in albumin fractionation

Any review of developments in albumin processing is hampered by the paucity of information; the detailed methods concern confidential industrial processes. For this reason, we will use the development of the albumin purification process at Bio Products Laboratory (BPL; a UK fractionator, which is part of the National Blood Service in England) to illustrate the general changes that have occurred in the industry over the past 20 yr. The albumin produced by BPL has long been of the standard required by the British Pharmacopoiea for human albumin solution, even though until the mid 1980s it was termed 'plasma protein fraction'.[21]

The Kistler and Nitschmann variant of ethanol fractionation[19] was introduced by BPL in 1964 and has remained the basis for production ever since, even though the scale has increased from a few tens of litres to over 6000 litres of plasma per batch. In the early days, the excess water and ethanol present in the albumin after cold ethanol fractionation were removed either by freeze-drying or, from the early 1980s, by thin-layer evaporative methods.[43] However, since 1987 this step has been carried out by the use of diafiltration technology, which is far less likely to result in protein denaturation than the previous methods.

Polishing improves purity

A chromatographic refining or 'polishing' step was also introduced into the BPL process in 1991 to further reduce concentrations of contaminant proteins and occasional high endotoxin concentrations. After diafiltration and adjustment to a suitable pH, the albumin solution is applied to a DEAE–Sepharose Fast Flow chromatography column, where impurities are bound and removed. The albumin, which is unretained, is then formulated, filled and pasteurized to produce the product known as Zenalb®, which has been in use for over 8 yr. The addition of this single anion-exchange chromatographic step produced marked improvements in the quality of the product. The purity of the albumin increased to ⩾99% and the monomer content to >95%. At the same time, concentrations of endotoxin and aluminium were consistently lowered, as shown in Fig. 2.

Whereas the introduction of a chromatographic polishing step has resulted in a major improvement in the albumin product, several other process changes, instituted over the past 10 yr, have also influenced purity and quality. The addition in 1992 of bulk pasteurization of the albumin before filling (whilst retaining the post-filling pasteurization step) has helped to control PKA concentrations during storage. The treatment of the plasma pool with the diatomaceous filter aid Celite, introduced in 1995, promotes the removal of PKA during the early fractionation process. Also, since 1997, aluminium concentrations have been further reduced by changing the type of glass used for the product container, a change widely adopted by other manufacturers.[17]

The net result of these process changes is a chromatographically purified human albumin solution that meets or exceeds the specifications set by regulatory bodies. The albumin remains undamaged during processing, contamination with non-albumin proteins is reduced to negligible concentrations, and the concentrations of PKA, endotoxin and aluminium are well controlled. This increased purity has enabled the shelf-life at room temperature storage to be extended. At the same time, the process for this very high purity albumin delivers a high yield within an acceptable processing time.

Clinical implications

The clinical importance of these product improvements has been demonstrated in the evaluation of patients undergoing therapeutic plasma exchange. In one comparison,[46] the incidence of product-related adverse reactions (defined as untoward changes in pulse, blood pressure or temperature) was markedly reduced from 1 for every 83 units infused (500 ml, 4.5% albumin) with the old BPL product to 1 for every 374 units infused with Zenalb 4.5. Likewise, in an initial assessment of Celite-treated albumin,[4] reduced numbers of febrile reactions were observed in comparison with the non-Celite-treated product (0.34 and 2.5%, respectively).

Albumin solution is generally well tolerated, especially in view of the size of the infusion volume. Adverse reactions have been reported in the scientific literature,[11 34] most notably when albumin has been used in plasma exchange. The tolerability of modern human albumin solution is illustrated by the incidence of spontaneously reported adverse reactions. Although such reporting underestimates the true incidence of adverse events, it provides a useful indication of a product's overall safety profile. Spontaneous reports received by the BPL Medical Department from various indirect sources (such as publications) or directly from individuals using Zenalb® suggest that the reported incidence of adverse reactions may be as low as 1 in 17 200 infusions for 4.5% albumin and 1 in 78 200 infusions for 20% albumin. Based on the information received, the adverse reactions were assessed by the BPL Medical

Department in terms of the seriousness of the reaction and the body system (e.g. cardiac, vascular, respiratory, neurological) affected (Table 2). None of the adverse events classified as serious in Table 2 was fatal. This level of incidence compares favourably with the 1 in 6600 incidence of adverse reactions to albumin reported by McClelland in 1990.[26]

Discussion

This review has concentrated on the methods of preparation and their relevance to the clinical use of albumin. Nevertheless, a number of papers have appeared over recent years which are critical of any significant role for albumin in therapeutic strategies, favouring other colloids or crystalloid solutions.[24 42 47] However, whereas Tjoeng and colleagues[42] recommend the use of synthetic colloidal supplements as an alternative to albumin, they do not discuss the adverse reactions which can occur to these alternatives, such as anaphylactoid reactions, problems with disordered coagulation and alterations in blood viscosity,[5 26 37] or their frequency, which may exceed those for albumin.[26]

Other workers have tried to critically assess the basis for the use of albumin in a variety of clinical conditions, and have classified albumin usage as being appropriate, unproven or inappropriate.[5 9 44 45] Whereas usage for certain clinical conditions has fallen, for others (e.g. meningococcal disease) albumin therapy is still the preferred treatment.[31] Other clinicians are unwilling to move away from the use of albumin in fluid replacement until the case has been proven by thorough clinical trials.[12 29] A recent study in cirrhotic patients with spontaneous bacterial peritonitis showed that antibiotic plus albumin had a significant benefit on conserving renal function and survival compared with antibiotic alone,[39] although whether synthetic plasma expanders would have been equally effective was not studied.

A number of adverse events have been reported to be associated with albumin therapy, including allergic (anaphylactoid) reactions, impairment of renal function, hypotensive reactions, cardiac problems and pulmonary oedema.[11 26 34] Anaphylactoid reactions to albumin occur relatively infrequently; they are likely to be due to a combination of subtle factors, including the sensitivity of the individual, the rate of infusion, and product characteristics. Problems with renal function and hypotensive reactions are thought to result from the presence of contaminants. Pulmonary oedema, resulting from the leakage of albumin into the extravascular space with its consequent osmotic effect on fluid accumulation, may be a result of inappropriate use. Rather than adhering to strict dosage regimens for albumin therapy, fluid and haemodynamic variables should be monitored carefully and therapy adjusted accordingly. In one report of pulmonary oedema occurring in children with nephrotic syndrome, the problem was assigned to too high an albumin dosage or too rapid infusion.[34] Indeed, the study of Lucas and colleagues,[22] who reported the greatest relative risk from albumin therapy, employed an extremely large 'fixed' dose of salt-poor albumin: 150 g during the operation and 150 g day^{-1} for the first five postoperative days. Margarson and Soni[24] have pointed out the error of chasing strict plasma albumin concentrations rather than using the amount of protein required to restore the colloidal osmotic balance. Some practitioners have distinguished, in their acceptance of albumin therapy, between high- and low-concentration preparations.[16] The tragic consequences of the inappropriate dilution of 25% human albumin have also been reported.[33]

After the publication of the Cochrane meta-analysis,[6] the use of albumin in the UK fell markedly.[36] Several authors have raised criticisms of the Cochrane meta-analysis itself, highlighting weaknesses in the performance of the review, failure to discriminate between data derived from patients with markedly different clinical conditions, and the grouping of data from trials with different clinical endpoints.[10 31 35 38] Indeed, Horsey[16] commented that there were only two explanations for the increased risk: that albumin had been given in excessive amounts or that it had become toxic as a result of commercial processing.

Some workers have suggested that the purity of the albumin preparations used may have influenced the results observed in clinical use, highlighting especially the toxicity of metal ions, in particular aluminium, which can be present in the products.[6 24] The aim of albumin processing is to provide a safe product whose properties mirror as closely as possible those of albumin found in plasma. This review has shown that, far from remaining unchanged over half a century, the process by which albumin is extracted from plasma and purified has undergone continuous improvement. As a result, albumin solutions for clinical use have been improved markedly, particularly in the past 20 yr. Modern processing technology ensures that damaged protein is removed and that concentrations of impurities such as PKA and aluminium are minimized. Such significant changes to the manufacture of human albumin call into question the validity of clinical studies performed over 20 yr ago. When making realistic assessments of the risks and benefits of albumin therapy to patients in intensive care, it is important to base such judgements upon experience with modern-generation products.[41] Some of the adverse reactions observed in the past may have been attributable to impurities that have since been eliminated or minimized by improved manufacturing technology.

It is also important to administer an appropriate dose of albumin, at a suitable rate, with careful monitoring of the patient's cardiovascular and pulmonary status. Although modern albumin solutions are closer than ever to the native substance, as with all therapeutic interventions there are inherent risks. With modern management techniques, such risks from albumin can be minimized and therapeutic gain achieved. Albumin is not just a fluid for hypovolaemia—

harnessing its carrier functions[32] is a positive challenge for the future.

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Conflict of interest

The authors are employed by Bio Products Laboratory (BPL), a unit of the National Blood Authority, a special Health Authority within the UK National Health Service. BPL manufactures a range of plasma-derived products, including human albumin solutions under the registered trade names Zenalb 4.5 and Zenalb 20.

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BJA

SHORT COMMUNICATIONS

Increased pre-operative platelet counts are a possible predictor for reduced sensitivity to heparin

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We investigated a possible relationship between pre-operative platelet count and reduced sensitivity to heparin in 87 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Sensitivity to heparin was determined by measuring the slope of the heparin dose response (HDR) before surgery. Pre-operative platelet counts were measured as part of routine analysis of the patients' coagulation status. Patients with an HDR slope of <80 s u. ml^{-1}, were considered to have a reduced sensitivity to heparin and activated clotting time data were collected from these patients before and after heparin administration before CPB. A significant correlation was determined between pre-operative platelet levels and HDR slope ($P<0.001$). Platelet counts were significantly greater in heparin-resistant patients compared with those who had the expected response to the anticoagulant ($P<0.05$). This could be caused by an increased capacity to produce platelet factor 4, which neutralizes heparin.

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In patients having cardiac surgery with extracorporeal circulation, sensitivity to heparin is important, because inadequate anticoagulation can disturb haemostatic mechanisms. Possible factors that contribute to heparin resistance include intra-aortic balloon pumping and pre-operative intravenous nitroglycerin therapy.[1 2] However, the most common reason is heparin treatment before operation, which can reduce concentrations of the coagulation inhibitor antithrombin III.[1]

Platelet counts are greater in heparin-resistant patients before operation, compared with those who are heparin-sensitive.[1 3] We studied the relationship between pre-operative platelet levels and the response to heparin in a population of patients undergoing cardiac surgery.

Methods and results

After local ethics committee approval and informed consent, eighty-seven patients presenting for either coronary artery bypass surgery (n=73), valve surgery (n=8) or a combination of both (n=6) were included in this study. Patients with pre-existing coagulopathy or who had received either warfarin (within 3 days of surgery), streptokinase (within 48 h), tissue-type plasminogen activator (within 48 h) or any antifibrinolytic agent (within 24 h) were excluded.

Platelet count, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured as part of the routine pre-operative evaluation of the patients' coagulation state. In addition, before surgery, the heparin dose response (HDR) for each patient was determined by the use of the Hepcon® Hemostasis Management System (Medtronic Inc, Minneapolis, MA, USA). This system carries out three dual channel clotting tests simultaneously by comparing a patient's blood with zero heparin in two channels, 1.5 u. ml^{-1} heparin in another two channels and 2.5 u. ml^{-1} heparin in the final two channels. As the response to heparin is linear up to 8 u. ml^{-1}, the three clotting times can be plotted on a graph to produce an HDR curve. The HDR slope (in seconds per unit heparin per ml of blood) is the value that the ACT will increase by, for every unit of heparin given per unit of ml blood volume. Patients with an HDR

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slope of <80 s u. ml^{-1} were considered to have a reduced heparin sensitivity and were studied further. Intra-operative administration of heparin was standardized in all patients and anticoagulation capacity was assessed by determination of ACT by the use of the Automated Coagulation Timer II® system (Medtronic Inc, Minneapolis, MA USA). If administration of 300 u. kg^{-1} heparin failed to achieve an ACT of ≥480 s, then a further 100 u. kg^{-1} of heparin was given. Patients were considered heparin-resistant if the ACT was <480 s after the second dose of heparin.

The Mann–Whitney *U* test was used to compare patient data. Where appropriate results are expressed as median (interquartile range). Correlation analysis was with Spearman's rank sum correlation.

Thirty patients from the original 87, had an HDR slope of >80 s u. ml^{-1} (group A). Of the remaining 57 patients, 42 achieved an ACT of ≥480 s after the first dose of heparin (group B), eight achieved an ACT of ≥480 s after the second dose of heparin (group C) and seven were heparin-resistant (Group D). Median (interquartile range) age and sex ratio (male: female) for each group were as follows: Group A (69 (62.5–73.8), 7:1); group B (68 (60–73), 5:1); group C (67 (65–78.8), 1:1) and group D (67 (64–70.5), 1:1).

A significant correlation was found between increased pre-operative platelet levels and a reduced sensitivity to heparin (as measured by the HDR slope) (P<0.001; Fig. 1). No correlation was observed for either the baseline ACT or the ACT after the first dose of heparin with pre-operative platelet levels. Pre-operative platelet count was significantly greater in patients in groups C (252 (221–270)×10^9 litre^{-1}) and D (262 (222–314)×10^9 litre^{-1}) compared with 194 (165–223)×10^9 litre^{-1} in group A (P<0.05). However, none of the patients had a pre-operative platelet count which was greater than normal levels (i.e. >400×10^9 litre^{-1}).

PT and aPTT values were within the normal range for all patients studied.

Comment

We found a significant correlation between pre-operative platelet count and a reduced sensitivity to heparin. In addition, pre-operative platelet counts were significantly higher in groups C and D compared with those in group A, although in these cases, platelet counts were within the normal range.

Platelets themselves are thought to influence the ACT, since anti-platelet agents can prolong clotting times. For example, abciximab, which binds to the platelet membrane glycoprotein IIb/IIIa receptor to inhibit platelet activation, can prolong ACT measurements in healthy volunteers.[4] However, in this study, there was no correlation between pre-operative platelet count and the initial ACT measurement suggesting that the baseline coagulation state of the patients was unaffected. In any case, low baseline ACT measurements are now not thought to be a predictor of heparin response.[1]

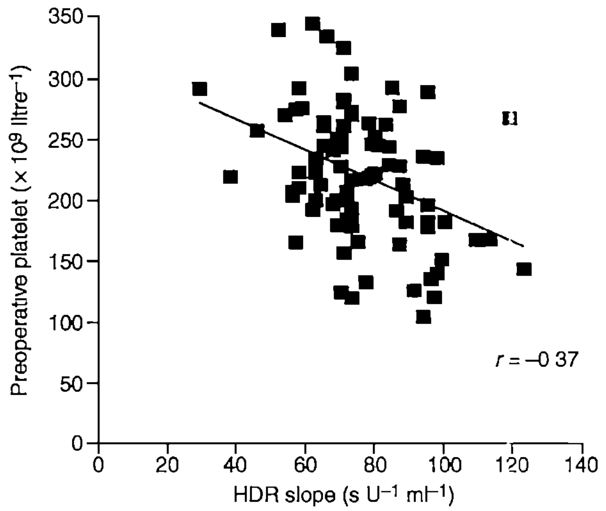

Fig 1 Correlation between preoperative platelet count and heparin dose response slope measured by the Hepcon® Hemostasis Management System

Patients with thrombocytosis, who have had surgery with CPB, require extra heparin to achieve adequate anticoagulation.[5] When activation of platelets takes place, they release platelet factor 4 and this neutralizes heparin. In fact, recombinant platelet factor 4 has been used in clinical trials as a possible alternative to protamine for antagonizing the anticoagulant effect of heparin.[6] Thus, patients with a higher platelet count would have a greater capacity to produce platelet factor 4 upon activation, which would have a heparin neutralizing effect. This would explain the correlation between pre-operative platelet counts and heparin response observed in this study.

However, heparin resistance is multifactorial and a high platelet count may indirectly reflect other processes The high platelet count could be an indirect reflection of more complex mechanisms related to ischaemic heart disease. These mechanisms may also induce a degree of heparin resistance that cannot be attributed to platelet factor 4 alone. Further studies are needed to allow a better understanding of the various components ultimately responsible for heparin resistance.

In conclusion, these findings present the possibility of using the assessment of pre-operative platelet counts could indicate patients who might have a reduced sensitivity to heparin.

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Prevention of postoperative nausea and vomiting by continuous infusion of subhypnotic propofol in female patients receiving intravenous patient-controlled analgesia

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In this prospective, randomized, double-blind, placebo-controlled study, the use of continuous subhypnotic propofol infusion as an antiemetic in fentanyl intravenous patient-controlled analgesia (i.v. PCA) was investigated during the first 24 h after surgery. One hundred female patients, ASA I–II, aged 20–71 yr, undergoing major gynaecological or orthopaedic surgery, were included. Either propofol 10 mg or placebo (1 ml of Intralipid) was given and one of the following five regimens was maintained for 24 h: propofol 5, 10, 15 or 20 μg kg^{-1} min^{-1} or Intralipid 1 ml h^{-1} as a placebo. Fentanyl i.v. PCA was started in the postanaesthesia care unit for postoperative analgesia. Significantly more of the patients given propofol 15 and 20 μg kg^{-1} min^{-1} experienced no nausea or vomiting compared with those given placebo (65% and 70% versus 25%; $P<0.05$). Patients given propofol 20 μg kg^{-1} min^{-1} reported more sedation than those in the other groups 4 h after surgery ($P<0.05$).

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Keywords: vomiting, nausea, postoperative; vomiting, antiemetics; anaesthetics i.v., propofol; analgesia, patient-controlled; analgesics opioid, fentanyl

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Postoperative nausea and vomiting (PONV) is one of the most common complications following anaesthesia and surgery. Although various antiemetics have been evaluated for the management of PONV, none of the currently available prophylactic antiemetic regimens are entirely successful.

The direct and indirect antiemetic effects of propofol are well known. As an anaesthetic, propofol has been associated with a lower incidence of PONV.[1] Propofol infusion in subhypnotic doses has been used successfully to manage chemotherapy-induced emesis.[2] Its efficacy for the prevention of PONV, however, has not been proven conclusively.[3,4]

This prospective, randomized, double-blind, placebo-controlled study was undertaken to investigate whether continuous subhypnotic propofol infusion would prevent PONV in female patients receiving fentanyl i.v. PCA and to determine the optimal infusion rates of propofol.

Table 1 Patient characteristics, incidence of post-operative nausea and vomiting (PONV), requirement for rescue antiemetics during the first 24 h, and sedation scores 4, 8 and 24 h after surgery. Values are mean (SD) when appropriate. *Significantly different from placebo ($P<0.05$), n.s.=no significant difference. Total fentanyl consumption dose includes i.v. PCA dose only. G=gynaecological surgery (total abdominal hysterectomy), O=orthopaedic surgery (posterior spinal fusion with instrumentation)

		Propofol				
	Placebo	**5 µg**	**10 µg**	**15 µg**	**20 µg**	***P* value**
n	20	20	20	20	20	
Age (yr)	52 (11.7)	49 (14.8)	46 (12.6)	48 (8.6)	50 (12.0)	n.s.
Weight (kg)	54 (5.3)	56 (9.2)	59 (6.4)	56 (6.8)	55 (5.7)	n.s.
Duration of anaesthesia (min)	181 (90.7)	182 (64.8)	177 (68.0)	171 (79.4)	175 (72.2)	n.s.
Total fentanyl consumption (µg)	413 (241)	585 (362)	537 (280)	514 (208)	712 (445)*	0.049
Surgery (*n*) (G/O)	9/11	9/11	9/11	9/11	10/10	n.s.
PONV (*n*(%))						
No symptoms	5 (25)	8 (40)	9 (45)	13 (65)*	14 (70) *	0.001
Nausea only	4 (20)	6 (30)	8 (40)	3 (15)	5 (25)	
Vomiting	11 (55)	6 (30)	3 (15)	4 (20)	1 (5)	
Rescue antiemetics (*n* (%))	5 (25)	2 (10)	3 (15)	1 (5)	0 (0)	n.s.
Sedation score						
4 h	1.15 (0.75)	1.30 (0.66)	1.30 (0.73)	1.50 (0.61)	1.75 (0.44)*	0.043
8 h	1.00 (0.73)	1.20 (0.77)	1.15 (0.81)	1.35 (0.75)	1.45 (0.76)	n.s.
24 h	0.30 (0.57)	0.55 (0.60)	0.50 (0.69)	0.60 (0.75)	0.55 (0.69)	n.s.

Methods and results

One hundred female patients (ASA I–II, aged 20–71 yr, weight 43–74 kg) undergoing either elective major gynaecological or orthopaedic surgery were studied. Patients undergoing different types of surgical procedure were distributed equally among the groups to minimize bias. Institutional ethics committee approval was obtained. Written informed consent was obtained before enrolment.

Patients who had significant systemic diseases, those who had vomited or received antiemetics within 24 h before surgery, and those with known allergy to propofol or a history of epilepsy were not included. Also excluded were those with high risk factors such as a previous history of PONV or migraine, or women who were menstruating.

On the day before surgery, patients and their care-givers were instructed in the use of an APII PCA pump (Baxter Healthcare Co., Deerfield, IL, USA) and in the use of the nausea/vomiting and sedation score card. They were told to ask for rescue antiemetics when PONV occurred. One hour before surgery, midazolam 3–5 mg and glycopyrrolate 0.2 mg were given intramuscularly. Anaesthesia was induced with thiopental 5 mg kg^{-1} i.v. and fentanyl 2–3 µg kg^{-1}, and maintained with enflurane, 50% nitrous oxide and oxygen. All received vecuronium 0.1 mg kg^{-1} to facilitate tracheal intubation and for subsequent intra-operative neuromuscular blockade. At the end of surgery, this was reversed with pyridostigmine 10 mg and glycopyrrolate 0.2 mg i.v.

Medication was blinded and randomized by our pharmacy, which delivered covered and coded vials of propofol or Intralipid. After patients had regained consciousness in the recovery room, a bolus of Intralipid 1 ml or propofol (Pofol; Je-Il Pharmaceutical Co., Seoul, Korea) 10 mg was given intravenously followed by continuous infusion of intralipid as a placebo or propofol using an infusion pump. Those given propofol boluses were randomly allocated to receive one of four infusion regimens for 24 h: continuous propofol infusion at 5, 10, 15 or 20 µg kg^{-1} min^{-1}.

All patients received fentanyl i.v. as postoperative analgesia via another PCA pump. The fentanyl concentration was 20 µg ml^{-1}, total volume 100 ml and bolus dose 20 µg; there was no basal infusion. The lockout interval was 6 min.

Droperidol 1.25 mg i.v. was to be administered promptly as a rescue antiemetic when requested. Patients and their care-givers were given score cards and asked to record the occurrence of nausea and vomiting. The investigator, blinded to the study drugs, verified the PONV episodes 4, 8 and 24 h after surgery and recorded sedation scores and other adverse side effects. Total fentanyl consumption during the first 24 h after surgery was recorded at the end of the study period. Pain scores were not measured in this investigation.

PONV was assessed on a three-point scale: 0=no symptoms, 1=only nausea, 2=vomiting. The highest score reported during the study determined the category to which a patient was allocated. Thus, patients who experienced both nausea and vomiting were included in the vomiting category. Sedation was evaluated on a five-point scale: 0=awake, 1=drowsy, 2=asleep but responds to verbal commands, 3=asleep but responds to physical stimulus, 4=unrousable.

Statistical analysis was performed with SPSS version 7.5 (SPSS Inc., Chicago, IL, USA). Discontinuous data were analysed using the chi-square test, and continuous data by one-way analysis of variance with Bonferroni correction for multiple comparisons between the study groups. A P-value of <0.05 was considered significant.

The results are presented in Table 1. All groups were comparable with regard to patient characteristics and type and duration of surgical procedures. Patients in the placebo group used significantly less fentanyl than those who received propofol 20 $\mu g\ kg^{-1}\ min^{-1}$ ($P<0.05$). Sixty-five per cent of the patients who received propofol 15 $\mu g\ kg^{-1}\ min^{-1}$ and 70% of those who received propofol 20 $\mu g\ kg^{-1}\ min^{-1}$ experienced no nausea or vomiting, compared with 25% of those who received placebo ($P<0.05$). Power analysis indicated that the sample size used here, 20 patients in each group, would be adequate to detect a 40% decrease in PONV with 90% power and an α error of 0.05.

Patients receiving propofol 20 $\mu g\ kg^{-1}\ min^{-1}$ reported more sedation than those receiving placebo 4 h after surgery ($P<0.05$). However, reported sedation levels did not differ significantly among the groups at 8 or 24 h. Other adverse effects, such as respiratory depression, were not observed.

Discussion

Patients undergoing major gynaecological or orthopaedic surgery with fentanyl i.v. PCA were chosen for this study because the incidence of PONV in this group is high.[5] Every attempt was made to match groups for factors known to affect the incidence of PONV, so it is highly likely that the observed differences between groups were mainly caused by the treatment.

Studies investigating the use of continuous subhypnotic propofol infusion for the prevention of PONV have produced conflicting results. Ewalenko and colleagues reported that subhypnotic propofol infusion at 1 $mg\ kg^{-1}\ h^{-1}$ effectively reduced the incidence of PONV from 65% to 10% without untoward sedative or cardiovascular effects after thyroidectomy.[3] Montgomery and colleagues[4] used a similar propofol infusion regimen but were unable to demonstrate any specific antiemetic effect over placebo. Our study showed that propofol infusion significantly reduced the incidence of PONV from 75% to 30%, similar to the results of Ewalenko and colleagues.[3]

There might be a therapeutic range of propofol concentration that prevents PONV. It has been shown that propofol for anaesthesia is associated with less PONV than volatile agents, but that it reduced only early PONV.[1] In previous studies on the management of chemotherapy-induced emesis and prophylaxis of PONV, 1 $mg\ kg^{-1}\ min^{-1}$ (17 $\mu g\ kg^{-1}\ min^{-1}$) has been used as the continuous subhypnotic dose of propofol infusion.[2] Recently, Gan and colleagues demonstrated that a plasma concentration of propofol at 343 $ng\ ml^{-1}$ was associated with 50% reduction in postoperative nausea.[6] Simulations indicated that a bolus dose of 10 mg followed by an infusion at approximately 10 $\mu g\ kg^{-1}\ min^{-1}$ are necessary to achieve this plasma concentration. Based on these reports, propofol infusion rates of 5–20 $\mu g\ kg^{-1}\ min^{-1}$ were selected for this study.

In our study, the patients who received propofol 20 $\mu g\ kg^{-1}\ min^{-1}$ were more sedated than those receiving placebo 4 h after surgery, even though none developed respiratory depression. This might have been related to residual sedative effects of inhalational anaesthetics and the concurrent use of fentanyl by PCA. Thus, continuous infusion of high dose propofol combined with opioids such as fentanyl should be carried out cautiously.

Fentanyl consumption in the placebo group was significantly less than that in the propofol 20 $\mu g\ kg^{-1}\ min^{-1}$ group. We feel that this was mainly because patients resisted pressing the button on the PCA pump, being afraid of aggravating PONV induced by PCA use.

Acknowledgements

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Intravenous anaesthesia and the rat microcirculation: the Dorsal Microcirculatory Chamber[†]

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The use of the dorsal microcirculatory chamber in male Wistar rats (*n*=7) to study the effects of induction and maintenance of anaesthesia on the microcirculation is described. Different patterns of responses were observed. At induction, arteriolar dilation was found following propofol and thiopental but ketamine produced constriction. During maintenance, constriction of arterioles was seen with ketamine and thiopental but dilation persisted with propofol The dorsal microcirculatory chamber appears to be a useful tool for the study of microcirculatory changes related to anaesthesia.

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Keywords: monitoring, microcirculation; anaesthetics i.v., propofol; anaesthetics i.v., ketamine; anaesthetics i.v., thiopental; rat

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Previous studies investigating the effect of anaesthesia on the microcirculation have been limited by the absence of a conscious control and the inability to measure the initial effects of agents in the absence of background anaesthesia. The major problem has been that it is not possible to observe these effects in microcirculatory beds that require surgical preparation without previously providing anaesthesia and analgesia.

We are describing the use of the Dorsal Microcirculatory Chamber (DMC) which allows serial study of the rat striated muscle microcirculation in the conscious state and during induction and maintenance of anaesthesia with different agents. The DMC is essentially a lightweight polycarbonate chamber enclosing a single layer of cutaneous muscle which is chronically implanted in the dorsal skin fold. This allows longitudinal studies using a number of agents in the same animal. The aim of this initial study was to evaluate the use of this technique by comparing the effects of induction and maintenance of anaesthesia with propofol, thiopental and ketamine with a conscious control on the striated muscle microcirculation.

Methods and Results

Seven male Wistar rats were entered into the study protocol which was conducted over a 10-week period. The studies were conducted under Home Office Licence PPL50/1252. During the first 2 weeks the rats were trained to sit at rest in the restrainer required for observation of the microcirculation. This familiarized the animals with the study environment thus minimizing any physiological effects of stress on the observations. At the start of the third week the DMC was implanted under fentanyl/fluanizone/diazepam (0.1 ml 100 g^{-1}) anaesthesia using the technique described by Smith *et al.*[1] and Hutchins *et al.*[2] Training in use of the restrainer was recommenced in weeks 4 and 5. The studies investigating responses to the different anaesthetic agents were conducted between weeks 6 and 10.

Each animal was studied on four occasions 1 week apart and received, in randomized order, either propofol, thiopental, ketamine or saline (control). The study protocol lasted 90 min. Animals were placed in the restrainer positioned on a horizontally mounted Nikon Optiphot 2 microscope (magnification 590×) equipped with transmitted light for observation of the microcirculation An area of muscle containing A1–A4 arterioles and V1–V4 venules was identified before starting the 90 min study period Vessels are classified by their order of branching, A1 being the largest (60–80 μm) with subsequent branching down to A4 (8–12 μm). Following a 30 min baseline period, anaesthesia was induced over 5 min and then maintained for a further 55 min. The area for observation was recorded on videotape, during transmitted light exposure, every 10 min for up to 30 s. The video images were subsequently analysed using a computerised image analysis system (Image Pro Plus, Media Ciberkinetics, USA) which allowed measurement (in μm) of change in vessel diameter.

[†] This study was presented, in part, at the British Microcirculation Society meeting in April 1999.

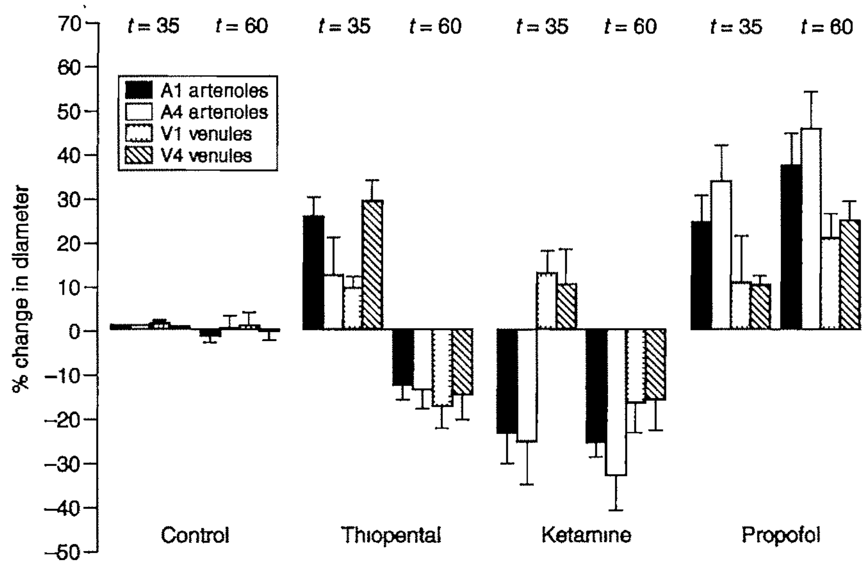

Fig 1 Change in vessel diameter (±SEM) as a percentage of t=30 min following induction (t=35 min) and during maintenance (t=60 min) with saline (control), propofol, ketamine and thiopental in A1 and A4 arterioles and V1 and V4 venules (n=7, P<0.05)

Measured changes in vessel diameter with each agent at the end of induction and during maintenance were compared with baseline (t=30), using Kruskal-Wallis and Wilcoxon Rank Sum tests (P<0.05 taken as significant). Kruskal-Wallis and Mann-Whitney U-test were used to compare changes produced by each agent with control study period.

Results are summarized in Figure 1 where the changes following induction (t=35) and during maintenance (t=60) are illustrated using A1 and A4 arterioles and V1 and V4 venules.

Control

Following 30 min baseline period, saline (2 ml kg^{-1}) was administered over 5 min via the tail vein followed by a continuous infusion at 5 ml kg^{-1} h^{-1} for the remaining study period. There were no significant changes in vessel diameter observed in any of the vessel groups throughout the 90 min study. There were no observed effects following either bolus or continuous infusion of saline. There were no significant changes from baseline during the control study period.

Thiopental

Anaesthesia was induced with a bolus of 30 mg kg^{-1} given over 5 min and maintained with a continuous infusion at 40–90 mg kg^{-1} h^{-1}. The diameters of all orders of vessels were stable during the baseline period. Induction of anaesthesia initially produced dilation of all arterioles (A1–A4) resulting in a 10–25% increase in diameter at the end of induction (t=35). The change was greatest in the A1 vessels. A similar magnitude of change was seen in the venules but V4 vessels dilated most.

During maintenance there was a change in all vessels (A1–A4, V1–V4) from dilation to constriction which occurred by t=50 and was maximal by t=60.

Ketamine

Anaesthesia was induced with a bolus dose of 30 mg kg^{-1} given over 5 min and maintained with a continuous infusion at 60–90 mg kg^{-1} h^{-1}. The diameters of all orders of vessels were stable during the baseline period. Induction of anaesthesia produced constriction of all arterioles and this was sustained throughout maintenance. This effect was evident at the end of induction (approximately 25% constriction). A different pattern of response was seen in venules where induction produced dilation and this changed to constriction during maintenance.

Propofol

Anaesthesia was induced with a bolus dose of 20–30 mg kg^{-1} given over 5 min and maintained with a continuous infusion at 20–60 mg kg^{-1} h^{-1}. The diameters of all orders of vessels were stable during the baseline period. Induction of anaesthesia produced a marked dilation of all arterioles (t=35, 20–40% change). Dilation continued throughout the maintenance period and tended to be greater in the smaller vessels (A3, A4) (NS). Venules dilated during induction, to a lesser extent than arterioles, and this dilation increased during maintenance.

With all agents the changes following induction and those during maintenance were significantly different from baseline (P<0.05). The changes during anaesthesia were all significantly different from control (P<0.05).

Comment

We have observed differences in the pattern of vessel diameter responses produced by the three anaesthetic agents used both at induction and during maintenance. The changes on induction are consistent with the known clinical effects of the drugs. Propofol and thiopental produced an initial dilation of vessels with the effect being greater following propofol, an effect that is in keeping with the decrease in arterial pressure that occurs at induction with these agents. There were differences in the pattern of changes with thiopental apparently having more effect on the larger arterioles (A1) and small venules and propofol having more effect on smaller arterioles and relatively less on venules. This is in agreement with the findings of our previous work on haemorrhage using a cremaster muscle preparation where dilation of small arterioles was more likely to occur along with lower arterial pressure.[3] However, the use of the DMC model will allow the mechanism of the anaesthetic effects to be explored more fully. The constrictor effect of ketamine is consistent with its known sympathomimetic effect. However, it is interesting to note an effect was observed in the small arterioles which are thought to receive less sympathetic innervation.

The findings of this study are in broad agreement with the limited number of studies of the effects of these agents on microcirculation with a conscious control. In a hamster skin fold model, propofol at an infusion rate of 78 mg kg^{-1} h^{-1} produced arteriolar and venular dilation.[4] In a bat wing model ketamine[5] caused dilation of arterioles but thiopental[6] had no effect on either type of vessel. *In vitro* studies have demonstrated vasodilation with all three agents.[7] The differences we have demonstrated within arteriolar and venular responses and between induction and maintenance may indicate a dose-dependent effect as shown in the studies with ketamine in a bat wing model.[5] We have previously shown that the doses used in this study produce a consistent light plane of anaesthesia.[3 8] However, the DMC model is capable of differentiating the responses to both induction and maintenance with a single agent as background anaesthesia is not required.

The DMC model provides a useful method for defining the microvascular effects of anaesthetic agents. It can be used to explore the relationship between microcirculatory changes and arterial pressure at induction of anaesthesia and the effect of different agents on the response to events such as haemorrhage or sepsis.

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Serotonergic receptor antagonists alter responses to general anaesthetics in rats

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Serotonergic neurotransmission is involved in controlling arousal levels in humans and other animals. Here, the effects of serotonergic receptor antagonists on the induction and depth of anaesthesia produced by three different general anaesthetics were investigated. Rats were pre-treated (i.p.) with either methiothepin (1.5 mg kg^{-1}), mianserin (5 mg kg^{-1}), ketanserin (7 mg kg^{-1}) or saline. Subsequently, successive, cumulative doses (i.p.) of either ketamine (final, cumulative dose of 350 mg kg^{-1}), sodium pentobarbital (final dose 77 mg kg^{-1}), or chloral hydrate (final dose 600 mg kg^{-1}) were administered. The response to the anaesthetics was measured using a behavioural test battery assessing nocifensive reflexes and hypnotic state. Pre-treatment with methiothepin enhanced responses to all three anaesthetics; mianserin enhanced responses to chloral hydrate. These results show that some serotonergic receptor antagonists change anaesthetic requirements, resulting in enhanced anaesthesia to hypnotics with different mechanisms of action.

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Keywords: anaesthesia, depth; anaesthetics i.v., ketamine; hypnotics barbiturate, pentobarbital; hypnotics, chloral hydrate; rat

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The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) plays an important role in the modulation of activity and arousal levels. Further, 5-HT is implicated in a variety of neurological and psychiatric diseases, and drugs that interact with the 5-HT system are commonly used in medical practice.[1] It is likely that altered serotonergic functioning, resulting from disease or serotonergic therapies, can influence responses to general anaesthetics. In rats, the anaesthetics ethyl ether, chloral hydrate, or urethane produce deeper anaesthesia, as judged by EEG responses to noxious stimuli, when they are combined with one of several 5-HT receptor antagonists.[2] Also, *in vitro* post-synaptic responses to 5-HT are reduced by some general anaesthetics, and this effect is potentiated by the addition of a 5-HT antagonist.[3] Thus, several lines of evidence suggest that, in the presence of 5-HT antagonists, the actions of anaesthetics are enhanced.

Here, a behavioural test battery was used to measure the responses to anaesthetics (ketamine, sodium pentobarbital, chloral hydrate), given to rats pre-treated with one of several serotonergic receptor antagonists. The antagonists used were methiothepin (which blocks a wide range of 5-HT receptors), mianserin (a more selective 5-HT_{1-2} blocker), and ketanserin (a highly selective 5-HT_2 antagonist), chosen based on their effectiveness to reduce EEG signs of arousal (see above). It was hypothesized that measures of behavioural arousal and responsiveness can demonstrate that rats with reduced serotonergic tone show an enhanced response to anaesthetics.

Methods and results

All experimental procedures were performed in accordance with guidelines of the Canadian Council on Animal Care and approved by the local Animal Care Committee. Male, adult (300–400 g) Long-Evans rats were brought from the animal colony (12–12 h light-dark cycle, testing done during the light phase) to a test room where they were left to habituate to the novel environment for 30 min. Subsequently, rats received injections (*pre-treatment*; i.p.; volume of 1 ml kg^{-1}) of one of the following compounds: saline, mianserin (5 mg kg^{-1}), methiothepin (1.5 mg kg^{-1}), or ketanserin (7 mg kg^{-1}; doses based on published[2] and unpublished experiments). Drugs were obtained from Research Biochemicals Inc. Canada, and dissolved in saline. Twenty-five minutes after pre-treatment, and continuing at 25 min intervals, different groups of rats received successive, cumulative doses of one of the following anaesthetics: ketamine (RBI; 7×50 mg kg^{-1}, total of 350 mg kg^{-1}); sodium pentobarbital (5×11, followed by 22 mg kg^{-1}, total of 77 mg kg^{-1}); and chloral hydrate (Fisher Scientific; 4×100, followed by 200 mg kg^{-1}, total of 600 mg

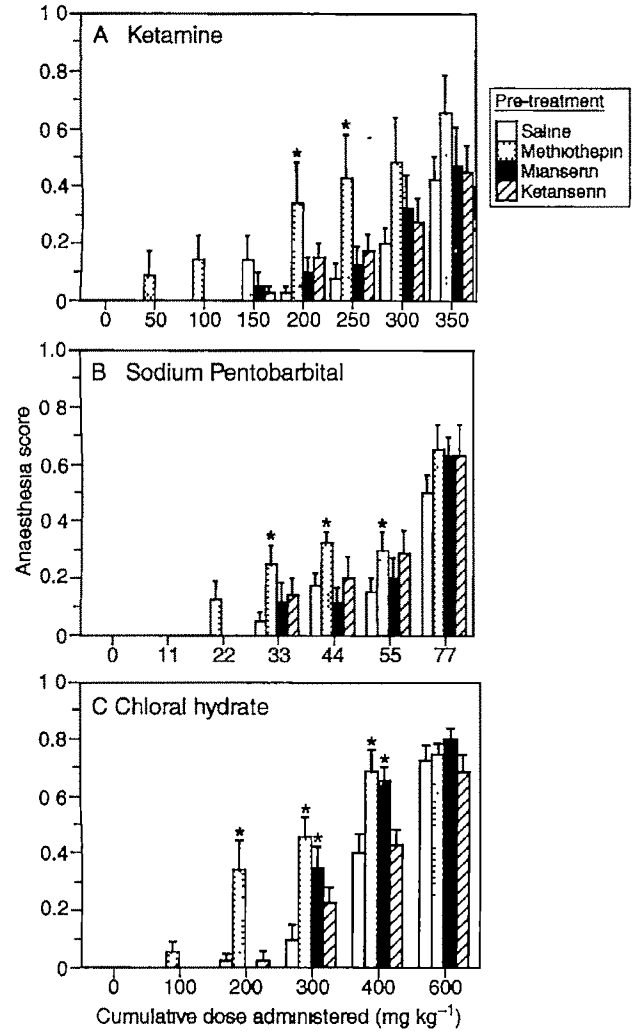

Fig 1 Effects of successive, cumulative injections (i.p.) of ketamine, sodium pentobarbital, or chloral hydrate on anaesthesia scores (higher score indicates deeper anaesthesia) in rats pre-treated (i.p.) with either saline (n=8), methiothepin (1.5 mg kg^{-1}, n=7–8), mianserin (5 mg kg^{-1}, n=7–8), or ketanserin (7 mg kg^{-1}, n=7–8) (A) Pre-treatment with methiothepin, but not with mianserin or ketanserin, resulted in a significant enhancement of ketamine anaesthesia (*$P<0.05$ relative to saline-treated rats, simple effects test). (B) Pre-treatment with methiothepin, but not with mianserin or ketanserin, resulted in a significant enhancement of pentobarbital anaesthesia relative to saline-treated rats (*$P<0.05$ against saline, simple effects test). (C) Methiothepin and mianserin, but not ketanserin, significantly enhanced chloral hydrate anaesthesia (*$P<0.05$ relative to saline-treated rats, simple effects test)

kg^{-1}). Each injection was given separately by inserting a 26 gauge needle into the intraperitoneal cavity.

Twenty minutes after pre-treatment and after each anaesthetic injection, the depth of anaesthesia was assessed by administering a battery of behavioural or reflex tests (in the same order as listed here): presence/absence of any spontaneous locomotion during a 1 min observation period; presence/absence of a righting reflex in response to being gently placed on the back; presence/absence of an eye-blink reflex in response to gently touching the cornea with the cotton tip of a Q-tip; absence/presence of a pinna reflex in response of touching the pinna with the wooden end of a Q-tip; presence/absence of limb or body movements in response to noxious stimulation in form of a tail pinch (attaching an alligator clip, sharp metal parts covered with electrical tape to avoid skin damage, 1 cm from the tip of the tail for 10 s). The presence or absence of a behavioural response were scored as a 0 and 1, respectively. These scores were then averaged across the five measures, and the resulting score was taken as the 'Anaesthesia Score' with higher scores indicating a deeper level of anaesthesia. Behavioural ratings were performed by an observer who was blind to the pre-treatment drug given to individual rats. Body temperature was monitored intermittently (every 10 min) with a rectal thermometer and maintained at 36–37°C by a heat lamp. Data are presented as mean (SEM) and were analysed by analyses of variance (ANOVA). In cases where ANOVA indicated a significant main effect of pre-treatment drug (i.e. saline or 5-HT antagonist), simple effect tests were computed to directly compare the two pre-treatment groups at each cumulative concentration of the anaesthetic (simple effects tests examine the effect of one factor, pre-treatment in this case, at one level of the other factor, anaesthetic concentration; see[4]). All statistical analyses were performed using the software package CLR Anova (Clear Lake Research Inc.).

Successive injections of ketamine produced a dose-dependent reduction in spontaneous and evoked behavioural responses (Fig. 1A; $F_{7,91}=21.1$, $P<0.001$). Rats pre-treated with methiothepin (1.5 mg kg^{-1}) showed a more rapid onset and deeper level of anaesthesia than rats pre-treated with saline, as indicated by an ANOVA main effect of pre-treatment (Fig. 1A; $F_{1,13}=4.9$, $P<0.045$). Pre-treatment with mianserin (5 mg kg^{-1}) or ketanserin (7 mg kg^{-1}) did not affect the rats' subsequent response to ketamine relative to saline pre-treatment (Fig. 1A; main effects of pre-treatment $F_{1,14}=0.8$ and 1.6, respectively, $P>0.2$).

The results obtained with pentobarbital were similar to those described above (Fig. 1B). Pre-treatment with methiothepin produced a deeper level of anaesthesia relative to saline following pentobarbital administration ($F_{1,14}=8.5$, $P=0.011$), but neither mianserin nor ketanserin produced this effect ($F_{1,13}=0.3$ and 1.2, respectively, $P>0.25$).

For chloral hydrate (Fig. 1C), both methiothepin ($F_{1,13}=11.3$, $P=0.005$) and mianserin pre-treatment ($F_{1,14}=7.9$, $P=0.014$) resulted in deeper anaesthesia relative to saline; ketanserin did not produce this effect ($F_{1,13}=0.4$, $P>0.5$). None of the pre-treatment drugs alone produced obvious indicators of anaesthesia.

Comment

The data presented here show that some 5-HT receptor antagonists can interact with different types of general anaesthetics. Information on interactions among 5-HT antagonists and anaesthetics is desirable to better predict potential adverse effects of anaesthetics in patients receiving serotonergic therapies.

In the present study, a behavioural test battery was used to assess the depth of anaesthesia. Results in agreement to those described here have been obtained using EEG methods in rats to assess anaesthetic status; EEG arousal responses to noxious stimuli (tail pinch) can be elicited under urethane or chloral hydrate anaesthesia, but they are reduced or absent if rats are given a combination of the anaesthetic and a 5-HT antagonist (e.g. ketanserin, ritanserin, methiothepin).[2] Thus, both behavioural and EEG measures suggest that 5-HT antagonists can enhance the action of general anaesthetics.

In addition to their serotonergic effects, the antagonists used here can interact with non-serotonergic receptors in the central and peripheral nervous system. Methiothepin and ketanserin both share an affinity for adrenergic and histaminergic receptors.[5] It is difficult to rule out contributions of non-serotonergic actions to the effects seen here; however, the fact that ketanserin was ineffective in potentiating the action of anaesthetics suggests that adrenergic and histaminergic binding did not contribute critically to this effect.

The present results are preliminary and a more thorough investigation of interactions between serotonergic antagonists and anaesthetics is required. For example, the mechanisms by which 5-HT antagonists interact with anaesthetics are not known, and it is not clear to what extent pharmacokinetic and metabolic factors contribute to the effects observed in the present study. It is of interest to note that a potentiation of anaesthetic effectiveness by a 5-HT antagonist has been observed *in vitro*.[3] This suggests that metabolic or pharmacokinetic changes alone may not account for the interactions between anaesthetics and 5-HT antagonists. Also, for all three anaesthetics tested, potentiation was seen during the earlier and/or intermediate, but not late stages of cumulative dosing (see Fig. 1). This observation provides indirect support for the hypothesis that differential clearing of the anaesthetic, or differences in the half-life of the 5-HT antagonists, both of which can be expected to have more pronounced effects in the later stages of a cumulative dosing experiment, may not be the sole, critical factors underlying enhanced anaesthesia with concurrent 5-HT antagonist treatment.

In summary, the available evidence suggests that serotonergic status can alter responses to general anaesthetics. Clinically, serotonergic antagonists (e.g. mianserin) are widely used to treat disorders as diverse as migraine, nausea, and depression.[1 6] An enhanced understanding of the interactions among serotonergic antagonists and anaesthetics should improve the anaesthetic management of patients receiving such drug therapies.[6]

Acknowledgements

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Sex and oestrous cycle differences in visceromotor responses and vasopressin release in response to colonic distension in male and female rats anaesthetized with halothane[†]

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Visceromotor responses and vasopressin release before and after colonic visceral distension were compared between male (n=5 (n=4 for vasopressin)) and female rats and between females during the oestrous cycle (proestrus n=6, oestrus n=5, metestrus n=5, diestrus n=6) at a controlled depth of anaesthesia. Pre-stimulation vasopressin and blood pressures demonstrated oestrous cycle variability. The mean (SEM) colonic balloon pressure triggering visceromotor responses was significantly higher in males (64 (4) mm Hg) than females (41 (1) mm Hg), P=0.002 and within females, proestrus rats had the lowest thresholds, (29 (1) mm Hg, P<0.01). Post-stimulation, vasopressin concentrations increased significantly in all groups (males 1.34 (0.39) to 2.24 (0.74) pmol litre^{-1}; females 1.54 (0.24) to 2.88 (0.58) pmol litre^{-1}; P=0.002). Within groups statistically significant differences were measured in proestrus 2.06 (0.56) to 3.42 (1.12) and oestrus 1.16 (0.38) to 2.76 (0.60) pmol litre^{-1} (P<0.05). High vasopressin concentrations coupled with low-pressure stimulation during proestrus shows sex-hormone dependent integration of the neuroendocrine response to noxious visceral stimulation.

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Aversive visceromotor and cardiovascular responses to visceral distension in animals can be measured repetitively using colonic balloon inflation[1] and are influenced in female rats by the oestrous cycle.[2] Confirmation of the relationship between vasopressin (AVP) release and noxious visceral stimuli is considered important in the understanding of stress responses as well as the fundamental differences between sexes and normal cyclical sex-hormone variations. The sensitivity and rapidity of AVP release coupled with a short half-life necessitates standardized experimental conditions that include gentle handling, specific time-related activities,[3] cardiovascular stability and controlled anaesthetic depth.[4]

It was hypothesized that AVP release could be stimulated by noxious visceral distension in anaesthetised rats and the magnitude of this response would vary with sex and oestrous cycle phase.

Methods and Results

Studies on 5 male and 4-day cycling female (6, 5, 5, and 6 in proestrus, oestrus, metestrus and diestrus respectively) adult Wistar rats were completed during the morning at the end of a 12 h dark cycle (Home Office PPL70/4211) using the method we previously described.[2] A saline vaginal smear was taken for cellular identification (a high proportion of cornified cells being present on the day of oestrus) to determine the oestrous phase.[5] This was read at the end of the experiment. Anaesthesia was induced with 5% halothane in oxygen then maintained with 2% halothane by a funnel closely applied to the airway. A calibrated Datex Capnomac II measured inspired halothane continuously at the nose. An 8 cm long double-lumen colonic balloon was fully inserted through the rectum into the colon and secured with tape, then a rectal thermometer to maintain normothermia. After securing the catheters the halothane concentration was reduced to 1%. The arterial catheter was connected via a strain gauge transducer to an Apple Macintosh Performa 475. Arterial blood pressures, with

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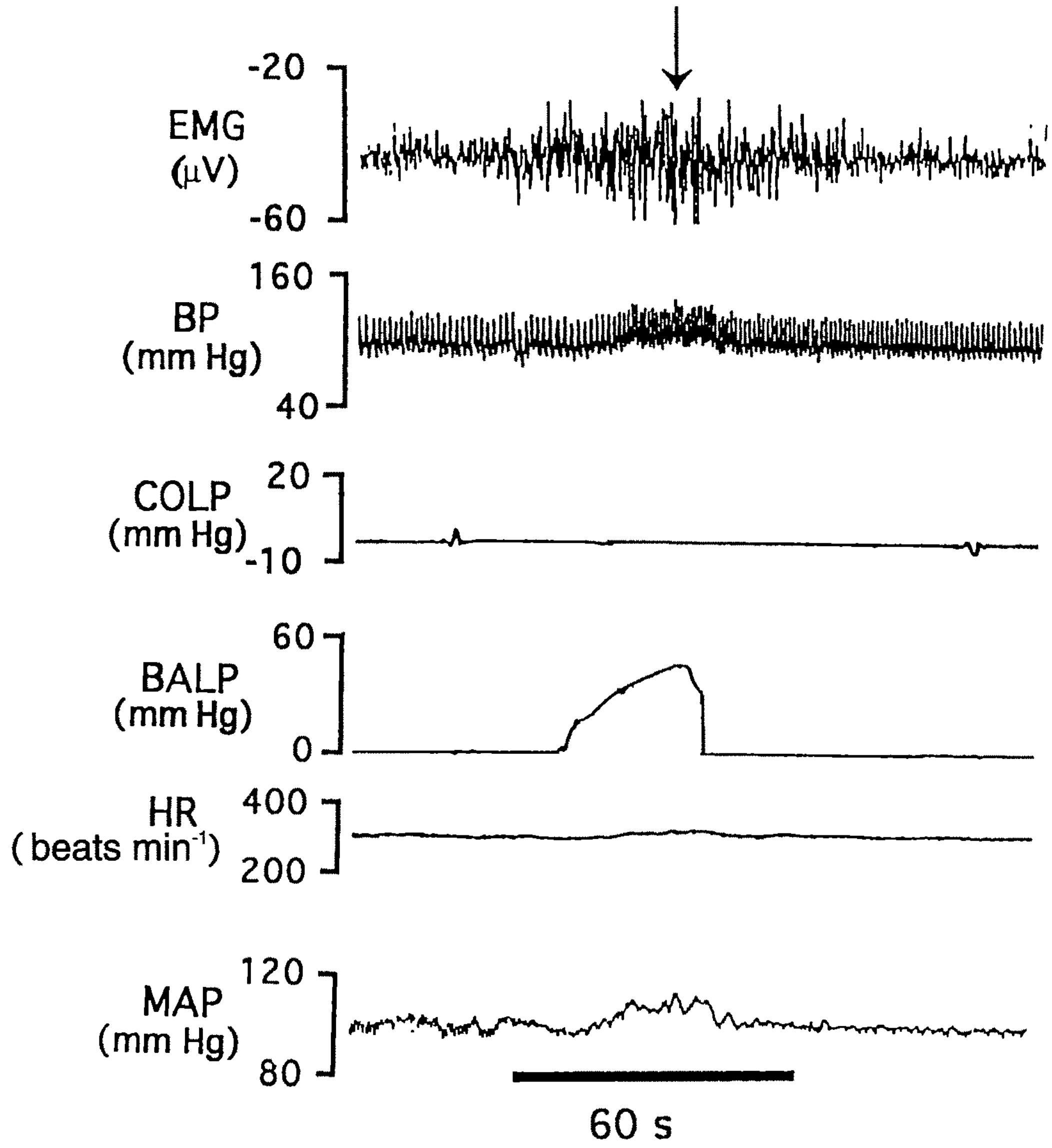

Fig 1 Measurements of the electromyogram (EMG), arterial blood pressure (BP), heart rate (HR), mean arterial blood pressure (MAP) and intracolonic pressure (COLP) showing the changes from baseline in response to a single colonic balloon distension (BALP) in a rat in metestrus. The arrow on the EMG trace corresponds with the balloon pressure that triggered a visual visceromotor response.

mean arterial pressures (MAP) and heart rates derived from it, and colonic balloon pressures were recorded as shown in Figure 1. Bilateral electromyography electrodes were connected to leg flexor muscles and the raw signal was used to confirm the onset of the visual visceromotor response.

After 20 min stabilization, volume replacement allowed 1 ml blood to be removed for AVP immunoassay. These sampling techniques do not lead to AVP release.[6] Vasopressin was determined by immunoassay in extracts of plasma prepared using C18 Sep-Pak columns (Waters Associates Ltd., Northwick, Essex, UK). Determinations were performed as described by Forsling and Peysner[3] using the First International Standard for AVP (77/501). The lower limit of detection for the assay was 0.12 (0.02) pmol litre^{-1} with intra and interassay variations of 7.7 and 11.9% respectively for 2.5 pmol litre^{-1}.

Colonic distension was achieved by slow manual balloon inflation (15–30 s), up to the threshold triggering the visceromotor response, with a 100 mm Hg maximum to prevent rupture, followed by deflation. Every 2 min threshold pressure and the associated MAP was measured. After six intermittent inflations, post-stimulation AVP and arterial blood gas analysis was taken and the rat killed by anaesthetic overdose. All rats had normal blood gases.

Mixed model ANOVA (Genstat, Numerical Algorithms Group, Oxford, UK) was used for three outcome variables: colonic pressure, MAP and AVP concentrations. Five

Table 1 AVP concentrations (pmol litre^{-1}), MAP and threshold balloon pressures (mm Hg) before and after stimulation by colonic balloon distension. All values are expressed as mean (SEM) (range). ^{a} Within groups: $P<0.05$, ^{b} between female groups $P<0.01$ (comparing each group to the diestrus group), between male and female groups: ^{c} $P<0.05$, ^{d} $P<0.01$

Groups	*n*	AVP (pmol litre^{-1})		*n*	MAP (mm Hg)		*n*	Balloon pressure (mm Hg)
		Pre-stimulation	Post-stimulation		Pre-stimulation	Post-stimulation		
Males	4	1.34 (0.38)	2.24 (0.74)	30	102 (2)	107 (2) $^{a\ c}$	24	64 (4)^{d} (36 - 94)
Females								
proestrus	6	2.06 (0.56)	3.42 (1.12) ^{a}	30	99 (2) ^{b}	102 (2) $^{a\ b}$	36	29 (1)^{b} (18–51)
oestrus	5	1.16 (0.38)	2.76 (0.60) ^{a}	30	97 (2)^{b}	103 (2) $^{a\ b}$	30	57 (3) (35 – 85)
metestrus	5	1.50 (0.60)	2.28 (0.80)	30	103 (2) ^{b}	108 (3) $^{a\ b}$	30	41 (2) (24 – 70)
diestrus	6	1.34 (0.34)	2.90 (1.42)	36	110 (2)	115 (1)^{a}	36	39 (2) (18 – 54)

groups were analysed, the four oestrous cycle phases within the female group and one male group. Cycle phase and time were taken as factors for inclusion in the model. The main results are presented as ratios of geometric means because log transformations were performed to comply with the assumptions of ANOVA. There were no statistically significant changes with time.

Baseline AVP concentrations, which lie in the normal physiological range for conscious rats,[3] and MAP are shown in Table 1. In all rats AVP increased post-stimulation. There were no significant differences in AVP concentrations (pmol litre^{-1}) between male and female groups (pre-stimulation mean (SEM): 1.34 (0.38) and 1.54 (0.24) respectively) with pre-stimulation male to female ratio of 1.167 (95%CI 0.539, 2.527; P=0.683). However, males have concentrations 17% greater than females. Similarly, post-stimulation the male: female ratio was 0.860 (95%CI 0.397, 1.863; P=0.689) with post-stimulation mean (SEM) values of 2.24 (0.74) and 2.88 (0.58) pmol litre^{-1} respectively. Although non-significant, males have concentrations approximately 14% smaller than females. Thus, over time, the magnitude of the change was smaller for males than females. The highly significant differences pre- and post-stimulation, taking males and females as one group, can be expressed as the ratio 1.941 (95%CI 1.309, 2.879; P=0.002). Thus the mean AVP concentration post-stimulation was 94% greater than the mean AVP concentration pre-stimulation. In addition, within the female group, after the colonic stimulation a statistically significant increase in AVP concentrations was detected in proestrus and oestrus.

Visceromotor responses were triggered at mean (SEM) balloon pressures for males and females of 63.8 (4) and 41.0 (1) mm Hg respectively. Proestrus rats have the lowest mean balloon pressure and males the largest. The ratio of males to females is 1.574 (95%CI 1.198, 2.068; P=0.002), so that the pressure to trigger a visceromotor response in males is approximately 1.6 times larger than females.

A significant sex difference in MAP exists post- but not pre-stimulation. The ratio of the geometric means in males to females, for pre-stimulation is 1.017 (95%CI 0.996, 1.038; P=0.113) and for post-stimulation 1.023 (95%CI 1.002, 1.044; P=0.031) with an average increase of 4%. When comparing MAP in females the most significant difference was between diestrus and the other groups. Pre- and post-stimulation diestrus rats had values 16–18% greater than either the proestrus or oestrus groups and approximately 5% greater than the metestrus group.

Comment

Pre-stimulation AVP concentrations confirmed the oestrous cycle variations originally described by Forsling and Peysner.[3] Although there were no statistical differences between males and females in baseline or post-stimulation AVP release despite the marked differences in balloon pressures required to elicit a visceromotor response, the magnitude of increase was smaller in males. The larger pressure for a visceromotor response and less AVP release may indicate that the hypothalamo-pituitary axis is more reactive in females than males. Metestrus showed least changes, which might be associated with a lack of hormonal changes during this phase. An increase in MAP with visceral stimulation is most likely to be the result of central nervous system stimulation in response to visceral afferent nerve fibre activity.[1] Noxious stimuli are associated with increased sympathetic nervous system activity causing hypertension. When MAP is elevated by non-hypothalamo-pituitary mediated mechanisms the response is to decrease AVP release. The increase in AVP release can be considered to relate to noxious stimulation rather than as a response to cardiovascular changes and possibly could be expected to be of greater magnitude if MAP was maintained at baseline values and did not increase with stimulation.

The higher balloon pressures observed in this study in males supports previous studies of sex differences in pain thresholds.[7] Autonomic nerves can transmit noxious stimuli from peripheral visceral structures to the hypothalamus. If afferent impulses can be traced to the hypothalamus, then what factors determine the variations in visceromotor and stress responses during the oestrous cycle? Evidence from double labelling immunocytochemistry demonstrates colocalization of oestrogen receptor beta with vasopressin in the supraoptic nucleus and paraventricular nucleus of the hypothalamus.[8] Electrophysiological changes in the frequency and intensity of peripheral nerve impulses from reproductive organs have also been shown during the oestrous cycle[7] particularly during proestrus and oestrus. These variations in peripheral nerve activity may modulate the central release of AVP, which is a stress hormone. In addition, central nervous system sensitisation may further modulate not only neural but also endocrine responses. Interactions between the central and peripheral neuroendocrine activity during noxious stimulation require further investigation.

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CASE REPORTS

Survivors of childhood cancers: implications for obstetric anaesthesia

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Treatment of many childhood malignancies involves surgery, radiotherapy and chemotherapy. If the child survives, normal physical development can be impaired and abnormalities with anaesthetic implications may be present. We discuss two women with a range of problems who presented for obstetric anaesthesia, having survived childhood malignancies. Common features included anthracycline cardiotoxicity and short stature. Both patients received incremental spinal anaesthesia in order to titrate the dose of local anaesthetic required to produce an adequate block height and to minimize cardiovascular instability.

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Modern, aggressive treatment of paediatric malignancies has enabled survival into adulthood. There is a small but increasing cohort of women of reproductive age who were treated with chemotherapy, radiotherapy and surgery in childhood. Although infertility and pregnancy loss are more common in such women, a significant number of them have successful pregnancies.[1] The consequences of chemotherapy, radiation and surgery will differ according to the site of the malignancy treated, but presentations in adulthood have common features. We present two women who survived childhood cancer and illustrate some of the difficulties that were encountered. The infants of both women were delivered by elective Caesarean section and both women requested regional anaesthesia.

Case 1

A 25-yr-old primipara presented to the anaesthesia clinic before elective Caesarean section at 34 weeks of gestation. At the age of 10 months, a mass around the right adrenal had been diagnosed as stage IV neuroblastoma. She had been treated with nephrectomy, adrenalectomy, radiotherapy and chemotherapy (vincristine, cyclophosphamide and doxorubicin). She was short in stature (145 cm, 4 ft 10 inches), and had a deformity of her right hip and a significant thoracolumbar scoliosis, which was not severe enough to limit respiratory function; pulmonary function tests had not been performed. She had suffered anthracycline cardiotoxicity, a dose-dependent complication of therapy with doxorubicin and daunorubicin. There was myocyte damage resulting from the production of free radicals, and cardiac growth was impaired.[2] Echocardiography 3 days before the operation demonstrated an ejection fraction of 45% and fractional shortening of 22%. Increasing breathlessness during pregnancy was ascribed to worsening cardiac function, for which she was taking lisinopril 7.5 mg daily. She was hypertensive (130/100 mm Hg), and methyldopa 250 mg twice daily had been added during pregnancy as the hypertension worsened. Renal function was normal. Because of her problems, her obstetrician had already chosen Caesarean delivery, and she requested regional anaesthesia. Two doses of dexamethasone 4 mg were given before delivery in an attempt to improve fetal lung maturity.

From the history and examination in the clinic, it was felt that reduced cardiac reserve posed the greatest anaesthetic problem, and that technical difficulty with regional block arising from scoliosis was a secondary concern. No respiratory problems were anticipated, and further investigations were not thought to be necessary. The plan agreed upon for anaesthesia was to use an incremental subarachnoid technique, with invasive arterial monitoring but without a pulmonary artery flotation catheter.

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Before operation, a 20-gauge cannula was inserted into the left radial artery, and a 16-gauge i.v. cannula was inserted into a forearm vein. An infusion of Gelofusine (B. Braun Medical Ltd, Aylesbury, UK) 500 ml was commenced. Further monitoring included ECG and pulse oximetry. In the sitting position, a 26-gauge Quincke spinal needle was inserted with difficulty into the L3/4 interspace. A 32-gauge catheter (TFX Medical, Lurgan, N. Ireland) was then inserted and the needle removed. Two centimetres of catheter was placed in the subarachnoid space. Initially, 0.5% w/v hyperbaric bupivacaine 1 ml and diamorphine 0.4 mg were injected whilst the patient was sitting. A further 500 ml of Gelofusine containing ephedrine 30 mg was commenced. The patient was then moved into a tilted left supine position. After 10 min, plain bupivacaine 2.5 mg was injected. Sensation was blocked up to T6 on the right and T4 on the left. Caesarean section was performed without incident. Transient hypotension (systolic pressure of 60 mm Hg) occurred on administration of a test dose of Syntocinon 1 IU, and no further oxytocic was given. A live female baby weighing 2 kg was delivered. Apgar scores at 1 and 5 min were 8 and 9 respectively, and the umbilical arterial pH was 7.36.

For postoperative analgesia, the patient received diclofenac 100 mg per rectum, and thereafter up to 150 mg orally per day, and paracetamol 1000 mg/codeine 60 mg as required to a maximum of six doses per day. The intrathecal catheter was removed in the recovery ward 2 h after operation. We continued invasive monitoring for 24 h after delivery and the patient was stable throughout this period. Blood loss at delivery was estimated at 500 ml, but the haemoglobin had decreased to 8.1 g dl^{-1} on the first postoperative day and 3 units of blood was transfused. The patient was seen by an anaesthetist for three consecutive days to identify complications of regional block. No such complications were apparent. The mother and baby were discharged home after 5 days. Antihypertensive medication was continued on discharge.

Case 2

A 24-yr-old primipara presented at 33 weeks for urgent Caesarean section with only a few hours' notice. The membranes had ruptured prematurely and markers of infection, especially raised C-reactive protein (11 mg $litre^{-1}$), were causing increasing concern about chorioamnionitis. The patient was apyrexial and had no other clinical signs of systemic infection. The patient had been treated successfully with radiotherapy and chemotherapy for rhabdomyosarcoma of the pharynx as a child. She had been informed that the treatment would result in infertility, so did not use contraception and the pregnancy was unplanned. She requested regional anaesthesia.

On examination she was of short stature (147 cm, 4 ft 11 inches) and had mandibular hypoplasia, which was considered likely to cause difficulty with intubation (Mallampati grade 2). There was little opportunity for further investigation. Cardiomyopathy secondary to an unknown anthracycline had been diagnosed previously and mid-trimester echocardiography demonstrated an ejection fraction of 60% and fractional shortening of 23%. Her medical history included fractured lumbar spine, for which no details were available. She was taking thyroxine because treatment had resulted in thyroid hypoplasia.

An incremental subarachnoid technique was chosen. In case regional anaesthesia was not successful, facilities for awake fibre-optic intubation were available. Before the block, monitoring with ECG, non-invasive arterial blood pressure and pulse oximeter were established. An i.v. cannula was placed in a forearm vein and Gelofusine 500 ml was given. In the absence of signs and symptoms of heart failure, invasive monitoring was considered unnecessary. Aseptic techniques were used, including gown, hat and mask. The skin was prepared with alcohol solution. We used a needle-through-needle technique with a Spinocath kit (B. Braun Medical, Melsungen, Germany). An 18-gauge Tuohy needle was placed in the epidural space and a 24-gauge catheter was threaded over a 29-gauge Quincke spinal needle passed intrathecally. Both needles were then withdrawn. An i.v. infusion of ephedrine 30 mg in Gelofusine 500 ml was begun with the first intrathecal injection. Three increments of 0.5% w/v hyperbaric bupivacaine were given (10 mg in total), together with 0.5% w/v plain bupivacaine 4 mg, and diamorphine 0.4 mg, without achieving a satisfactory block. At this point it was decided that the tip of the catheter might be positioned in a caudad direction and the catheter was withdrawn 2 cm. Hyperbaric bupivacaine 0.5% w/v 2.5 mg and 0.5% w/v plain bupivacaine 5 mg were then given, producing excellent anaesthesia with abolition of sensation bilaterally to T5. There was no haemodynamic disturbance, and the patient was stable throughout. A female baby was delivered, and the umbilical arterial pH was 7.28. Syntocinon 10 units was given slowly via the i.v. infusion on delivery, without detectable hypotension. Prophylactic cefuroxime 750 mg and metronidazole 500 mg were given i.v. in the operating theatre and continued orally for 5 days. Postoperative analgesia consisted of diclofenac and paracetamol/codeine. The estimated blood loss at delivery was 700 ml. The intrathecal catheter was removed in the recovery ward. The next day, haemoglobin was recorded as 9.8 g dl^{-1} and 3 units of blood was transfused. An anaesthetist visited the patient for 3 days to identify complications of regional blockade. The mother and baby were discharged home after 5 days.

Discussion

Despite different original pathologies, these two survivors of paediatric malignancy have common features.

Anthracycline cardiotoxicity

Anthracyclines are a family of cytotoxic antibiotics. Anthracycline cardiomyopathy is a dose-dependent complication of therapy with doxorubicin and daunorubicin, which damages myocytes and impairs cardiac growth.[2] If given in childhood, normal cardiac growth is impaired, leading to permanent cardiac dysfunction. The toxicity has been attributed to the production of free radicals. The incidence of cardiomyopathy after chemotherapy is unknown, and whether a safe dose exists has not been clarified. Changes are irreversible and are characterized by a poorly compliant myocardium[3] that is likely to respond poorly to changes in preload and afterload. Diagnosis is made clinically, using echocardiography or cardiac catheterization, but may be confirmed histologically, showing hypertrophy and fibrosis of myocytes.[3] Both our patients had impairment of left ventricular function, but one woman was symptomatic with breathlessness, indicating a degree of cardiac failure. Her limited cardiac reserve presumably accounted for the hypotension after administration of 1 unit of Syntocinon. We did not think it advisable to give a further dose. Our second patient, despite a fractional shortening of 23%, was asymptomatic and tolerated Syntocinon well. Clinical assessment correctly identified which woman posed the greater risk. The long-term prognosis of this condition may be poor, and transplantation has been required.[4]

Scoliosis and short stature

Scoliosis can be a cause of short stature. In our first case, the scoliosis was presumed to be secondary to radiation-induced hip deformity. The spine may also be affected during the irradiation of midline tumours,[5] and deformity, white matter injury, osteoporosis and epidural space scarring has been documented.[5] Norris recommended one dose of single-shot intrathecal local anaesthetic for regional block, assuming normal anatomy, but of the 50 women included in that study only one was less than 150 cm tall.[6] Scoliosis and short stature can cause uncertainty about the dose of intrathecal local anaesthetic required. Our solution to potential problems within the epidural space is to use an intrathecal approach, and because of uncertainties over dose we titrated the local anaesthetic through an indwelling catheter. This had the added advantage of a slow onset of block, avoiding cardiovascular upset.[7] An additional factor in our choice was that we have significant experience with Caesarean delivery in scoliotics using continuous intrathecal anaesthesia.[8]

Oxytocics

Oxytocics are used to provide uterine contraction and haemostasis after delivery. Two drugs are commonly used for this purpose: ergometrine and Syntocinon, singly or in combination. Ergometrine, an ergotamine alkaloid, is a powerful oxytocic but is known to raise systemic vascular resistance significantly and increase afterload.[9] Syntocinon, a synthetic form of the naturally occurring oxytocin, has greater cardiac stability, but is known to cause hypotension with bolus administration.[10] The mechanism for this is debatable. Possible causes are a reduction in venous pressure, a decrease in vascular resistance, and negative inotropy, or a combination of these.[10] Death at Caesarean section has occurred after bolus administration of Syntocinon in a woman with congenital heart disease.[11] Our experience demonstrates that even minute doses of Syntocinon can cause worrying hypotension in the presence of poor myocardial function. It has been suggested that slow infusion of Syntocinon may reduce the incidence of hypotension.[9] Cardiac output monitoring is justified when effects are predicted to be severe.

Survivors of childhood cancers will present with increasing frequency for obstetric anaesthesia both to regional centres and to district general hospitals. It is likely that these women will have abnormalities affecting anaesthesia and a management plan should be made in the antenatal period. Adult survivors with lifelong cardiac impairment secondary to anthracyclines are an emerging problem. The first exposure of young adult cancer survivors to anaesthesia may occur with their first pregnancy, and the obstetric anaesthetist may be the first to test cardiac performance and to deal with the sequelae of their treatments.

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Prolonged vecuronium neuromuscular blockade associated with Charcot Marie Tooth neuropathy

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Charcot Marie Tooth (CMT) disease comprises a group of disorders characterized by progressive distal muscle weakness and wasting. Review of the anaesthetic literature produced conflicting reports concerning the responses to neuromuscular blocking drugs in these patients. We describe a case in which vecuronium 0.11 mg kg^{-1} produced prolonged neuromuscular blockade lasting 115 min in a patient with the condition. Conduction velocity in the facial nerve is usually less affected than the ulnar or peroneal nerve in CMT patients. This nerve may be more useful in monitoring neuromuscular blockade, both in titrating the dose of neuromuscular blocking drug and ensuring adequate reversal at the end of a procedure. Recent advances in molecular biology have enabled identification of the underlying genetic abnormalities and pathophysiology of CMT. These advances are reviewed and implications of CMT for the anaesthetist discussed.

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Charcot Marie Tooth (CMT) neuropathy affects 1 in 2500 people and accounts for a large proportion of the neuropathic diseases encountered in clinical practice.[1] The condition causes atrophy and weakness of the distal muscles due to diminished nerve conduction. The spectrum of severity varies from asymptomatic individuals to those with severe limb abnormalities requiring corrective surgery.

There are few descriptions of the anaesthetic management of patients with CMT. Both prolonged and attenuated responses to neuromuscular blocking drugs have been described.[2-5] Such variation between patients may be accounted for by variations in disease severity. Autosomal dominant and X-linked genetic defects may occur in these patients, resulting in point mutations or multiple expression of genes encoding myelin proteins.[6] Axonal loss or demyelination occurs, enabling classification of CMT according to nerve biopsy and conduction studies.[7] CMT is now considered to be a heterogeneous group of polyneuropathies. The severity of symptoms may differ between the subtypes.

It is appropriate to review recent advances in our understanding of the condition and the anaesthetic experience that has been described.

Case report

A 59-yr-old, 74 kg male with CMT neuropathy presented with a fractured right proximal fibula and distal tibia, requiring open reduction and internal fixation with a tibial nail. The patient had been diagnosed as having CMT in May 1987 in a medical report for retirement on the grounds of ill health. The diagnosis was made on clinical grounds, with examination revealing high foot arches and distal muscle wasting involving the forearms, interossei in the hands, and all muscles below the knee. His arm tendon reflexes were brisk and symmetrical but knee and ankle jerks were absent with flexor plantar responses. Sensation was normal and there was no ataxia. He described himself as always having been weak. He had no siblings but described his father as having been of the same build. Electromyography had not been performed.

The patient underwent L5-S1 discectomy in 1983, receiving thiopental 225 mg, tubocurarine 40 mg and halothane. The operation lasted 75 min. There was no comment in the anaesthetic record regarding reversal of residual neuromuscular blockade, nor were any problems recorded. In 1996, he underwent insertion of a dynamic hip screw of his left femur and received midazolam 2 mg, propofol 100 mg, and atracurium 30 mg at

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induction followed by atracurium 10 mg after 30 min. This operation lasted 50 min. Acetylcholinesterase inhibitors were not given. On neither occasion was any neuromuscular monitoring used. No adverse events or clinical evidence of prolonged neuromuscular block were noted.

After his hip fracture, a diagnosis of osteoporosis was made using bone density studies. He received alendronate 10 mg day^{-1} and calcium supplementation. His corrected serum calcium was 2.59 mmol litre^{-1} with an inorganic phosphate of 1.00 mmol litre^{-1} prior to this operation. Serum potassium was 4.6 mmol litre^{-1}.

On this occasion the patient was unpremedicated. He received morphine 10 mg and thiopental 350 mg at induction. Vecuronium 0.11 mg kg^{-1} was administered and after 2 min the trachea was intubated easily with a size 9 mm cuffed oral tracheal tube. Anaesthesia was maintained with isoflurane 1% in nitrous oxide/oxygen 2:1. No further opiates were given. A peripheral nerve stimulator was not used at the outset because no problems had been identified from the previous anaesthetic records.

The operation lasted approximately 115 min, during which time no further drugs were given. At the end of the procedure the lungs were ventilated with $F\text{I}_{\text{O}_2}$ 1.0 and the patient received neostigmine 2.5 mg with glycopyrrolate 500 µg. A peripheral nerve stimulator was not used at this stage. It was felt that sufficient time had passed since induction for recovery from neuromuscular blockade to occur. Spontaneous diaphragmatic breathing with an adequate tidal volume followed and the tracheal tube was removed uneventfully although the patient was not fully conscious. He was then transferred to the recovery room with oxygen administered by facemask. In recovery, the patient became anxious and distressed, with signs of incomplete reversal of neuromuscular block including twitching of the limbs and uncoordinated movements. Oxygenation and ventilation remained normal.

A peripheral nerve stimulator was applied first to the right ulnar nerve. Trains of four stimuli were applied. There was a palpable twitch response to the first stimulus only. As clinically obvious muscle wasting was present in the forearm muscles the nerve stimulator was applied to the right facial nerve. Again, a twitch response was only visible to the first stimulus of the train of four. Double burst stimulation was not used as partial reversal was clinically obvious and it was felt this would subject the patient to further distress.

A second dose of neostigmine 2.5 mg was given, resulting in all four twitches of the train of four response in the facial muscles being visible within 2 min. The patient's condition improved and he was transferred to the high dependency unit for overnight observation and returned to the ward on the next day.

Discussion

Charcot Marie Tooth neuropathy comprises a heterogeneous group of peripheral nerve diseases affecting adults and children.[7] There is a typical clinical picture with distal muscle weakness and atrophy affecting the intrinsic muscles of the foot, the peronei and tibialis anterior. Both motor and sensory function may be affected. Deep tendon reflexes are diminished or absent. There is a spectrum of clinical presentation from severe atrophy with limb abnormality to pes cavus. A significant proportion of CMT patients are not identified because their symptoms do not cause them to consult a doctor. Most patients with the condition have manifestations by their second decade, seldom presenting after 30 yr. Upper limb involvement tends to occur later.

Clinical studies in CMT families using nerve biopsies and nerve conduction studies enabled a separation of these patients into two main groups.[8] In CMT1 there is a marked reduction in nerve conduction velocity with demyelination; nerve conduction velocity in the ulnar, median and peroneal nerves is commonly half that in normal subjects.[7] The muscle action potential amplitude is half normal, and the nerve latency three times as long on average; 25% of patients have clinically thickened peripheral nerves. Those adolescents with the slowest conduction velocities tended to have a worse neurological deficit in later life.

In CMT2 the nerve conduction velocity is normal or low normal.[9] There is axonal loss but no prominent demyelination. In this type the clinical symptoms may present later, even in middle age. Although the features are similar to CMT1, there is said to be less upper limb involvement and the peripheral nerves are less enlarged.

The two types cannot be distinguished solely on clinical grounds because there is such a range of severity of symptoms. Nerve conduction studies are often performed in the median or ulnar nerves because distal nerve degeneration is often complete in the lower limbs. In fact, motor nerve conduction velocity is commonly less than 60% normal in all nerves studied, including the facial nerve.

Advances in molecular biology and gene mapping have enabled the underlying genetic abnormalities in CMT to be identified. In the majority of cases of CMT1 and CMT2 the inheritance is autosomal dominant.[10] There are also much rarer X-linked and autosomal recessive variants. CMT1 can be subdivided on the basis of the gene defect. In CMT1a there is a duplication at the 17p11, 2–12 locus. This area codes for the PMP22 gene resulting in multiple expression. PMP22 is a major component of peripheral nerve myelin. The result may be a new Schwann cell phenotype that has defective myelin stability and increased turnover.[10] In CMT1b there are point mutations in the myelin protein P0 gene.[6] This codes for the major myelin protein in peripheral nerves, accounting for 50% of the mass. It has been suggested that the neurological disability in CMT1b is worse than in CMT1a. In X-linked CMT (CMTX), which is clinically similar to CMT1, there are mutations in the connexin 32 gene. This encodes a gap junction channel protein that may play a role in transmission at nodes of Ranvier. Dejerine Sottas disease, or CMT3, is a severe variant with onset in infancy. There may be point mutations in the P0 or PMP22 genes. The clinical features overlap with severe CMT1. CMT2 accounts for 25% of cases.[9] There does not appear to be a unifying genetic defect.

As 1 in 2500 people has some form of CMT, it is surprising that case reports concerning anaesthesia in CMT sufferers are rare. In one report, the notes of seven patients under 16 yr who were anaesthetised over a 10 yr period were reviewed.[11] These patients received both depolarizing and nondepolarizing neuromuscular blocking drugs. There were no recorded adverse effects of succinylcholine and no cases of prolonged response to a range of non-depolarising neuromuscular blocking drugs. However, the authors conceded that the methods used to assess neuromuscular function varied widely.

Antognini reviewed the operative charts of 86 patients with CMT identified by postal questionnaire to members of a CMT help group.[12] In 161 surgical procedures on these patients anaesthetic complications were few, although the study is necessarily biased because non-responders are excluded. In addition, anaesthetic management and inclusion criteria for CMT could not be standardized. 48% of patients received succinylcholine with no recorded adverse effect. A paralysing dose of non-depolarizing neuromuscular blocking drug was used in 45% of patients. How neuromuscular block was monitored and reversed is not known. There were no descriptions of objective weakness or prolonged intubation. Despite the absence of adverse effects after succinylcholine, it would seem prudent to avoid this drug in CMT if possible as hyperkalaemia is well reported in other similar polyneuropathies and denervation injuries. There is no evidence to suggest that patients with CMT are susceptible to malignant hyperthermia.

Another report studied 20 patients with CMT presenting for orthopaedic procedures.[2] The authors found that CMT sufferers required less thiopental for induction than controls. The report is of interest because one female patient received vecuronium 0.07 mg kg^{-1} at induction and subsequently did not exhibit a normal twitch response or spontaneous ventilation for 280 min. In addition, the ulnar nerve twitch response was absent in six of the 20 patients. In these six patients, the facial nerve was used for evaluation of neuromuscular block.

A review of the literature concerning anaesthesia for CMT revealed few detailed case reports. One describes prolonged artificial ventilation due to respiratory muscle involvement in pregnancy.[13] Another describes a 17-yr-old who underwent anaesthesia on two occasions and showed no prolonged response to either mivacurium or atracurium.[3] Baraka described a 16-yr-old girl who underwent a tendon transfer under general anaesthesia using vecuronium. In this case, the T4/T1 ratio recovered to 25% after 20 min and further supplementation was required. Residual neuromuscular blockade was readily reversed after 90 min. The author suggested that upregulation of acetylcholine receptors at the neuromuscular junction due to the generalized polyneuropathy might account for the resistance to vecuronium even in the presence of muscle weakness and atrophy.[4]

One case report demonstrated a potential difficulty in monitoring neuromuscular block in CMT patients. In a 17-yr-old neurosurgical patient, it was not possible to elicit responses from either tibial nerve following vecuronium 0.1 mg kg^{-1} after 100 min. The muscle response was either too delayed or too small in amplitude to be recorded.[5] This is perhaps unsurprising as the tibial nerves are among the worst affected by demyelination in CMT. The use of peripheral nerve stimulators in CMT has been shown to be misleading if a nerve with delayed conduction or increased latency is chosen. One solution would be to monitor relaxation after induction using a less affected peripheral nerve such as the facial nerve. A suitable site for neuromuscular monitoring should be identified before a neuromuscular blocking drug is administered. The drug can then be titrated to effect and adequate reversal identified.

Case reports have been described in the literature of patients with CMT undergoing central neural blockade without neurological sequelae.[14 15] Posterior column demyelination has been noted in autopsies of some CMT patients, however. A balanced risk assessment in considering central blockade would seem prudent lest any deterioration be blamed on the anaesthetic technique. Autonomic neuropathy is not a major finding in CMT. It is usually limited to decreased sweating in the extremities. Autonomic neuropathy does not feature as a clinical problem in any anaesthetic case reports.

Clinically palpable nerve enlargement occurs in 25% of patients with CMT 1. These patients may be at greater risk of positional nerve injuries due to pressure during prolonged procedures. In addition, the use of regional blockade in areas such as the elbow may carry additional risk.

Given the incidence of CMT and the fact that many cases go unrecognized, it would seem that anaesthesia for these patients must be generally uneventful. The cases presenting for corrective limb surgery must be the worst affected and yet adverse events are seldom described.

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Severe unilateral bronchospasm mimicking inadvertent endobronchial intubation: a complication of the use of a topical lidocaine Laryngojet injector

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A healthy young woman is described in whom the left chest was unable to be inflated after intubation. The differential diagnosis and management are discussed. Severe unilateral bronchospasm was probably caused by topical lidocaine injected at the vocal cords and, inadvertently, into the left main bronchus with a Laryngojet device.

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A healthy 19-yr-old woman, weighing 64 kg, was scheduled for angiography and alcohol sclerosis of a facial arteriovenous malformation. She had no history of chest disease but smoked 10 cigarettes per day.

She received no premedication. Anaesthesia was induced slowly with midazolam 1.5 mg and propofol 110 mg, during which time she breathed oxygen. Anaesthesia was maintained with an infusion of propofol at 660 mg h^{-1} initially, reducing to 500 and 400 mg h^{-1} at 15 and 25 min respectively. Neuromuscular block was obtained with vecuronium. Before laryngoscopy, 40 mg of lignocaine was given i.v. A clear view of the larynx was obtained. The tip of a Laryngojet lidocaine (4%) injector was passed about 2 cm through the glottis, so that about half of the side-holes were above and half were below the cords. Five millilitres of solution were injected and the trachea was intubated with a 7.5 mm reinforced tracheal tube which was secured at 21 cm at the lips. On immediate inspection, both sides of the chest appeared to inflate equally and capnography revealed a normal waveform. The patient was transferred to the adjacent x-ray table and was ventilated with oxygen and air (FI_{O_2} = 0.35) via a Bain system and a Nuffield 200 ventilator with a tidal volume of approximately 600 ml. Within 2 min of intubation the Sp_{O_2} had fallen from 100 to 90%. The inspired oxygen fraction was increased to 1 and the chest was re-examined. The right chest was expanding and breath sounds were vesicular with no wheeze. On the left, there was no expansion and there were no breath sounds or added sounds at all. Inadvertent right-sided endobronchial intubation was suspected. The tube position was rechecked. It remained at 21cm at the lips. The tube tip was checked immediately by dynamic x-ray screening and was

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seen 2 cm above the carina. A suction catheter was passed blindly down the tracheal tube. No secretions were aspirated and the left chest remained silent. The whole chest was then screened on X-ray. The right lung was seen to expand and accommodate the entire tidal volume. On the left there was no inflation of any lobe. The left hemidiaphragm was motionless and there was some basal collapse. Pneumothorax was excluded. Because the ventilatory abnormality was unclear, the procedure was discontinued, and a bronchoscopy was done to exclude an obstruction in the left main bronchus. This showed a normal bronchial tree on both sides to the level of the segmental bronchi, and no appreciable secretions.

The left chest remained static. The Sp_{O_2} 20 min after intubation remained at 90% with an FI_{O_2} of 1, and the basal collapse had increased.

Fifty micrograms of salbutamol was given intravenously. The PE'_{CO_2} rapidly increased from 5.2 to 6.3 kPa after 2 min. The alveolar plateau of the capnogram changed from virtually flat, to markedly up-sloping. The pulse rate increased from 85 to 110 min^{-1}. There was now very slight expansion of the left chest and a marked expiratory wheeze. A further 50 µg of salbutamol was given. Within 3 min, expansion of the left and right chest was equal. The PE'_{CO_2} decreased to 5.0 kPa within a further 3 min and the capnogram plateau became almost flat again. The inspired oxygen fraction was reduced to 0.35 and the Sp_{O_2} remained at 98%. Given this marked improvement, the angiography proceeded and sclerosis of the arteriovenous malformation was done, taking approximately 1 h. After this, repeat screening of the chest showed both lungs expanding equally and complete resolution of the previous left basal collapse. The patient was extubated uneventfully and returned to the ward, where she was monitored closely. She displayed no wheeze or gas exchange deficit.

Discussion

Failure to ventilate one side of the chest after intubation of the trachea occurs commonly. Routine examination of the chest by inspection and auscultation after intubation will identify this and allow treatment before complications result. The most likely cause is unilateral endobronchial intubation, which is easily remedied by withdrawal of the tip of the tube into the trachea.

In this case, it was unlikely that the tip of the tube was beyond the carina because its position at the lips seemed to be normal for the size of the patient. If attempts had been made to withdraw the tube until the left chest began to expand, this could have caused inadvertent extubation at a time when this could be least afforded. We had a unique radiographic opportunity to examine the causes and consequences of this incident without altering the tube position. Screening the tube tip position confirmed the initial clinical belief that it was in the trachea. Screening the whole chest showed no air entry to the left lung. If this were caused by large airway obstruction, say a large mucous plug, then it would have to be very proximal indeed. Blind passage of a suction catheter was predictably unhelpful and bronchoscopy excluded any airway obstruction as far down as the segmental bronchi.

The patient's oxyhaemoglobin saturation remained at 90% with an FI_{O_2} of 1. This is consistent with venous admixture of the order of 40–50%.[1] The development of the basal atelectasis is of interest. Atelectasis in dependent dorsal regions is well known to occur during anaesthesia.[2 3] It can occur very rapidly (within minutes) when patients have been preoxygenated[4] or when lungs containing regions with a very low ventilation/perfusion ratio (V/Q) are ventilated with a high FI_{O_2}. Atelactasis is not easily visible on conventional X-ray imaging, but is detected with high sensitivity by CT scanning.[5] This patient was only partially pre-oxygenated. However, when the oxyhaemoglobin saturation fell after intubation, the FI_{O_2} was increased to 1. The whole of the left lung probably had a low V/Q, and the dependent dorsal regions more so. Even with screening that was relatively insensitive, atelectasis was noted and evolved over 20 min. In this case, the ventilatory abnormality was gross and unlikely to be missed. However, with a less obvious abnormality, if an increase in FI_{O_2} restored a nearly normal Sp_{O_2}, a prolonged anaesthetic might be permitted to proceed. Indeed, some anaesthetists use an FI_{O_2} of 1 routinely. In such cases, the progressive development of atelectasis might impair postoperative lung function and gas exchange.[6]

There are three cases of 'unilateral bronchospasm' listed in Medline (1966–2000). Two occurred after surgical procedures of the pleura (interpleural analgesia and pleurodesis)[7 8] and one after subclavian vein puncture. Shantha[7] reviews the likely mechanisms for unilateral bronchospasm. Bronchomotor tone depends on the balance of β-adrenergic and vagal parasympathetic outflow. Unilateral bronchospasm could result from (i) disproportionate sympathetic blockade, or (ii) stimulation of superficial airway receptors supplied by vagal fibres by any irritant.[7] A direct sympathetic nerve supply to the bronchial smooth muscle has been questioned[9] and it is unlikely that sympathetic blockade occurred in this case. The lignocaine given i.v. would be unlikely to cause significantly large plasma concentrations, nor would it act unilaterally, and the topical lignocaine is unlikely to have penetrated such a deep and distant structure as the hilar plexus. The topical lignocaine may have stimulated airway receptors to produce vagally mediated bronchoconstriction. Atelectasis by a local neural bronchoconstrictor reflex can occur after a variety of lung insults, including pulmonary embolism and trauma.[10] Constriction is not limited to the conducting airways, but is thought to be effected within the alveolar acinus by specific contractile interstitial cells, which are thought also to control local pulmonary capillary blood flow and hence exert an effect on V/Q matching.[11]

Downes and colleagues[12 13] showed that, in dogs, both aerosolized and i.v. lignocaine prevented the increase in airway resistance produced by an irritant citric acid aerosol, suggesting that lignocaine by either route blocked the reflex irritant response. They also showed that aerosolized lignocaine did not prevent allergic bronchospasm produced by inhalation of *Ascaris* antigen in previously sensitized animals. By contrast, Fish and Peterman[14] showed that, in eight asthmatic subjects, rather than blocking reflex bronchoconstriction, aerosolized lignocaine (4%) actually caused it. They conclude that whilst topical lignocaine is theoretically capable of blocking neurogenic reflexes, it may produce reflex bronchoconstriction in patients with asthma or hyperirritable airways.

This patient was not asthmatic and had no history of recent upper respiratory tract infection. She was, however, a smoker and could have had hyperirritable airways. In addition, the drug was administered not as aerosolized mist but as a jet of liquid, which itself is likely to be more irritant. This case demonstrates a problem of a topical lignocaine delivery device which is capable of depositing a relatively large dose of the drug below the cords, and sending a jet of drug down either main bronchus or even both bronchi. It also demonstrates a risk of high inspired fractions of oxygen (in this case obligatorily) when the lung has significant areas with very low V/Q ratios. The fortuitous use of instant X-ray screening allowed the tube position to be exonerated, and the value of fibre-optic bronchoscopy in the differential diagnosis is highlighted.

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Anaesthesia for Kartagener's syndrome

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Kartagener's syndrome is a hereditary syndrome involving a combination of dextrocardia (situs inversus), bronchiectasis and sinusitis, transmitted as an autosomal recessive trait. We describe a patient who had three anaesthetics over a period of a few months. Discussion relates to anaesthetic considerations in the syndrome and to recent findings relating to the molecular mechanisms of left-right development.

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A 27-yr-old female presented for surgery three times. She had Kartagener's syndrome.[1] The first operation was a left middle lobectomy for bronchiectasis. Some months later she complained of abdominal pain and her second operation revealed an ovarian adenocarcinoma. This operation was complicated by an episode of postoperative pneumonia. Two weeks later she had a total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Case report

The first operation—left middle lobectomy

The patient's main complaint was one of recurrent episodes of pneumonia. She also admitted to chronic sinusitis and volunteered the information that 'her heart was on the wrong side but normal'. Examination revealed no clubbing; her apex beat was on the right side; auscultation of the heart sounds was normal and there were some crepitations and rhonchi mainly in the left axilla.

Chest x-ray revealed dextrocardia and a right-sided stomach bubble. ECG demonstrated sinus rhythm and inversion of the P wave in lead 1 with a deep Q wave and inversion of the T wave. CT scan showed bronchiectasis that was most prominent in the left middle lobe. Lung function tests were normal and it was not considered necessary to do a blood gas study. She was admitted to the clinic for physiotherapy and scheduled for left middle lobectomy.

Anaesthesia for thoracotomy and lobectomy was unremarkable apart from it seemed logical to use a right-sided double lumen tube as she had three lobes on the left and two on the right with the longer main bronchus on the right. General anaesthesia was induced with propofol and maintained with isoflurane and sufentanil. For neuromuscular block we used vecuronium. Routine monitoring was enhanced by inserting a radial arterial line. The trachea was intubated with a right-sided 37 FG Mallinkrodt double-lumen tube and the lungs ventilated with a Servo Elema 900C ventilator.

After surgery, the trachea was extubated and the patient returned to the ward. Her postoperative course was uneventful and she was sent home after a few days.

The second operation—diagnostic laparoscopy

A few months later after the lobectomy the patient presented to a gynaecologist with abdominal pain. We were not involved with her management at this time. She had a general anaesthetic for laparoscopy that revealed adenocarcinoma of the ovary. Her postoperative course was complicated by an episode of left lower lobe pneumonia.

The third operation—total abdominal hysterectomy and bilateral salpingo-oophorectomy

Two weeks after the laparoscopic examination, the patient presented for total abdominal hysterectomy and bilateral salpingo-oophorectomy. In view of the fact that her last procedure had been complicated by pneumonia, spinal anaesthesia was chosen. She was sedated with midazolam 5 mg i.v. Spinal anaesthesia was given through a 25-gauge pencil point needle using 12.5 μg of hyperbaric bupivacaine. A continuous propofol infusion was used for sedation. Surgery was performed through a Pfannenstiel incision. The operation and postoperative period was uneventful.

Discussion

Kartagener's syndrome is a variant of the immotile cilia syndrome.[2] This has also been called primary ciliary dyskinesia and is a result of an autosomal recessive disorder of the microtubules of ciliated cells. Symptoms include male sterility, chronic or recurrent respiratory tract infection, and bronchiectasis because of the absence of mucociliary clearance. In 50% of patients situs inversus occurs and hence Kartagener's syndrome.

It may become possible to link the occurrence of abnormal ciliary function and abnormal position of the body organs. It seems that genes determine the structure, function, and time of appearance of proteins in the embryo that influence normal development and siting of the internal organs asymmetrically (situs solitus). On the left side of the embryo, near Hensen's node, a variety of proteins are secreted (Sonic Hedgehog, Nodal, Lefty and Pitx2). On the right side are others (Activin betaB, Snail and Fibroblast Growth factor-8).[3] These normally influence rotations, that lead to a left-sided heart and the usual position and structure of the lungs and abdominal organs. Abnormal genes and so abnormal proteins would lead to malpositions. Normal ciliary motion in the mouse node is anticlockwise and conceivably influences the flow of the proteins to their correct sites in the embryo. In the immotile cilia syndrome it is possible that abnormal distribution of the proteins occurs. Is this the reason that the dextrocardia of Kartagener's syndrome links with the immotile cilia syndrome, and also situs inversus?

The anaesthetic implications of Kartagener's syndrome are varied. The anaesthetist might be involved with patients who have sinus surgery, pulmonary surgery, infertility investigations or possibly cardiac surgery. Of primary importance will be assessment of pulmonary and cardiac structure and function, and also prevention of pulmonary complications in the bronchiectatic patient.

Physiotherapy, postural drainage, antibiotics, bronchodilators and incentive spirometry all have a role perioperatively. Where possible, local or regional anaesthesia is to be preferred to general anaesthesia. In thoracic surgery, the anatomy of the bronchi should be considered before selecting a double lumen tube.

Knowledge of the position of the abdominal organs and of the branching pattern of the main stem bronchi is important in categorizing malpositions; and these must be borne in mind. When dextrocardia occurs with situs inversus, the heart is most frequently normal. When dextrocardia occurs without situs inversus, when the visceral situs is indeterminate (situs ambiguus), or if isolated levocardia is present, associated, often complex, multiple anomalies are usually present.[4] Dextrocardia with complete situs inversus occurs in approximately 2 per 10 000 births. The incidence of congenital heart disease is low being about 3%. Kartagener's syndrome will occur in about 20% of patients.[5] Thus, the incidence being approximately 1 in 50 000 births. Our patient did not have an echocardiogram and on clinical grounds was assumed to have a totally normal heart.

In contrast, dextrocardia with situs solitus or situs ambiguus is less common (1 per 20 000 births) and the incidence of congenital heart disease is extremely high, probably 90% or greater. Dextrocardia with situs solitus usually, although not invariably, associates with severe complex cardiac abnormalities. They are most commonly transposition of the great arteries, double outlet right ventricle, ventricular septal defect, single ventricle and pulmonary stenosis or artresia.[5] In patients with dextrocardia and situs ambiguus, polysplenia or asplenia may be present in association with complex multiple cardiac abnormalities. These include a combination of systemic and pulmonary venous abnormalities, defects in the ventricular and atrial septa and endocardial cushion defects.

There may be pulmonary artery obstruction and maldevelopment of the great arteries.[6]

The incidence of isolated levocardia (a left-sided heart) with situs inversus is about 0.6% per 10 000 births and more than 90% have serious heart disease.[5]

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Acute right-to-left inter-atrial shunt; an important cause of profound hypoxia

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Three patients presented to our intensive care unit over a 3-yr period with profound hypoxia resulting from acute right-to-left inter-atrial shunt (RLIAS). Patient 1 was a 67-yr-old male with an atrial septal defect who became hypoxic and developed the rare sign of platypnoea following elective repair of an abdominal aortic aneurysm (breathlessness made worse when upright and relieved by lying flat). Patient 2 was a 38-yr-old female who developed platypnoea and

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hypoxia secondary to a patent foramen ovale (PFO) and pericardial effusion. Patient 3 was a 46-yr-old male with a PFO who developed hypoxia without platypnoea because of multiple pulmonary emboli following right hemicolectomy. These case reports illustrate the need to consider RLIAS as a cause of hypoxia of sudden onset. Early use of bubble contrast echocardiography is indicated.

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Shunting of blood across a defect between the two sides of the heart is usually directed by the left-to-right pressure gradient. A large and persistent left-to-right shunt can increase pulmonary blood flow, which over months or years leads to microvascular changes, increased pulmonary vascular resistance and elevated pulmonary artery pressure. When the pulmonary arterial pressure approaches the systemic arterial pressure, the direction of the shunt reverses (the Eisenmenger syndrome). This chronic development of right-to-left shunt (RLIAS) is accompanied by electrocardiographic changes of atrial enlargement and right ventricular hypertrophy. Chest radiography reveals prominent pulmonary arteries.[1]

In contrast, the adult patient with an asymptomatic inter-atrial defect may develop an acute RLIAS following a cardiac or respiratory insult. Acute RLIAS is a separate clinical entity from the Eisenmenger syndrome. Acute RLIAS is often overlooked as a cause of hypoxia[2] but early diagnosis can direct therapy and avoid unnecessary invasive investigations. The three cases reported here illustrate the need to consider RLIAS in the differential diagnosis and investigation of profound hypoxia.

Case reports

Patient 1

A 67-yr-old man presented for elective repair of an abdominal aortic aneurysm. He had a past history of hypertension, transient ischaemic attacks and a left hemiparesis from which he had made a full recovery. His exercise tolerance was good and a preoperative multiple uptake-gated acquisition scan demonstrated a left ventricular ejection fraction of 67%. Anaesthesia and surgery were uneventful. The perioperative cardiac index was 3–4 litres min^{-1} m^{-2} and pulmonary arterial pressures ranged between 28/8 and 52/24 mm Hg. He required admission to intensive care unit (ICU) 3 days postoperatively with hypoxia (Pa_{O_2}=5 kPa) on room air, pulmonary oedema, blood pressure of 90/60 mm Hg and oliguria. He required tracheal intubation, positive pressure ventilation, diuretics and inotropes. His oxygenation improved, allowing tracheal extubation after 3 days but after 10 days his Pa_{O_2} was 5.65 kPa and Pa_{CO_2} 2.7 kPa on a FI_{O_2} 0.95. He also developed platypnoea; that is he was unable to sit upright because of severe breathlessness but he was less breathless when lying flat, particularly in the left lateral decubitus position.

Initially the underlying cause of this patient's hypoxia was not clear. Transthoracic echocardiography (TTE) demonstrated good left ventricular function, mild mitral regurgitation and septal hypertrophy. A lung perfusion scintographic scan showed no evidence of pulmonary embolism. Thoracic computerized tomography revealed non-specific bilateral shadowing of the lung fields consistent with adult respiratory distress syndrome (ARDS) or infection. Despite antibiotic therapy followed by a trial of prednisolone 70 mg day^{-1} for possible ARDS, he continued to deteriorate and required reintubation and positive pressure ventilation. A pulmonary artery flotation catheter demonstrated a cardiac index of 2.1 litres min^{-1} m^{-2}, mean right atrial pressure of 8 mm Hg, mean pulmonary arterial pressure of 37 mm Hg and pulmonary artery occlusion pressure of 3 mm Hg. During inspired nitric oxide therapy at 20 p.p.m. the cardiac index increased to 3.8 litres min^{-1} m^{-2}, the mean right atrial pressure was 4 mm Hg, mean pulmonary arterial pressure 34 mm Hg and pulmonary artery occlusion pressure 5 mm Hg. The Pa_{O_2} increased from 10.5 to 24.5 kPa on a FI_{O_2} 1.0.

A cardiology opinion was sought concerning the possibility of an inter-atrial shunt, but this diagnosis was thought to be excluded by the absence of a persistent right-to-left pressure gradient; right atrial pressure range of 4–8 mm Hg with a pulmonary artery occlusion pressure range of 3–5 mm Hg. However, an inter-atrial defect was discovered fortuitously during pulmonary angiography when a catheter passed from the right atrium into the left atrium. Bubble contrast transoesophageal echocardiogram (TOE) demonstrated RLIAS with severe impairment of right ventricular function (Fig. 1).

The patient became septicaemic and died on the 26th postoperative day. Post-mortem examination revealed a secundum ASD, absent superior vena cava and anomalous venous drainage via a dilated coronary sinus. The right ventricle appeared normal and the lungs were oedematous. On histological examination, there was mild pulmonary fibrosis but no features of ARDS, organizing pneumonia, or pulmonary hypertension.

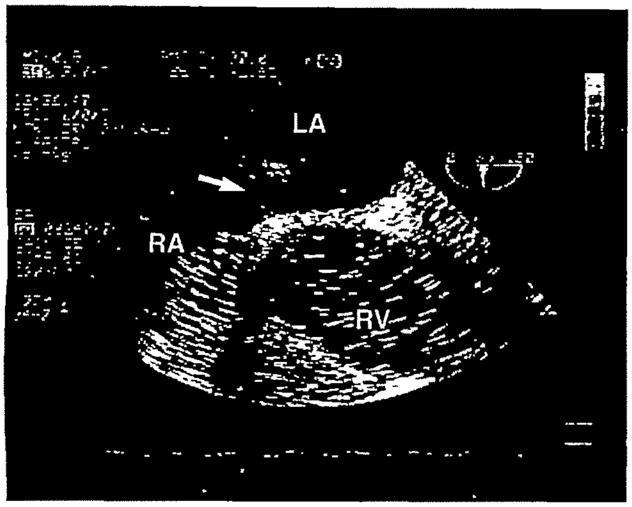

Fig 1 Transoesophageal echocardiogram using bubble contrast (Patient 1) Injected microbubbles are seen as white specks. The bubbles visible in the left atrium (LA), at the same time as the right atrium (RA) and right ventricle (RV), are indicative of RLIAS An ASD is seen (arrow).

Patient 2

A 38-yr-old woman presented with platypnoea and cyanosis that developed over a period of 4 days. Sitting upright exacerbated her breathlessness and she was more comfortable when lying flat despite being profoundly hypoxic. She had a past history of chronic renal impairment and aortic incompetence. At presentation she was an inpatient recuperating from an episode of infective endocarditis and gastrointestinal bleeding for which she had required treatment in the ICU.

On physical examination she was apyrexial, heart rate 110 beats min^{-1}, arterial pressure 120/80 mm Hg and the jugular venous pressure was not elevated. An aortic murmur was present, but unchanged from previous examinations; respiratory rate was 20 b.p.m. and chest auscultation was normal. Arterial blood gases on a FI_{O_2} 0.6 were: pH 7.6, Pa_{O_2} 5.6 kPa, Pa_{CO_2} 3.8 kPa, base excess 6.3 mmol litre^{-1}. A chest radiograph showed a small right pleural effusion. Lung perfusion scintographic scan demonstrated a single segment perfusion defect in the right mid-zone. A preliminary diagnosis of pulmonary embolism was made but the decision to anticoagulate was deferred until a pulmonary angiogram could be performed in view of her recent history of gastrointestinal haemorrhage. During pulmonary angiography, the catheter passed through a patent foramen ovale into the left atrium and left upper lobe pulmonary vein. Radio-opaque dye flowed from the right to the left atrium. Pulmonary arteriography demonstrated no emboli. Mean pulmonary arterial pressure was 12 mm Hg and mean right atrial pressure was 13 mm Hg compared with 8 mm Hg in the left atrium. Right atrial PO_2 was 2.8 kPa and the left atrial PO_2 was 5.5 kPa. Transthoracic echocardiogram revealed a right-sided pericardial effusion, 4.5 cm in depth, compressing the right ventricle. Left ventricular function was good. Pericardial tap brought immediate relief of the patient's hypoxia; the Pa_{O_2} rising from 5.8 to 30.4 kPa, on oxygen 10 litres min^{-1} by facemask.

Patient 3

A 46-yr-old man presented with breathlessness 4 days after right hemicolectomy for caecal carcinoma. Axillary temperature was 38.5°C, he had a sinus tachycardia 135 beat min^{-1}, arterial pressure 90/60 mm Hg and a respiratory rate of 32 breath min^{-1}. Pa_{O_2} was 4.1 kPa and Pa_{CO_2} 4.2 kPa on room air. Oxygen at maximum flow via a facemask did not improve his hypoxia and he was transferred to ICU. FI_{O_2} 0.9 with CPAP 5 cm H_2O produced a Pa_{O_2} 7.5 kPa. The patient was not distressed despite his hypoxia and was able to tolerate lying flat for a pulmonary angiogram. Pulmonary angiogram revealed a large embolus in the left-upper lobe pulmonary artery with smaller emboli in the right middle lobe pulmonary artery and right pulmonary vessels peripherally. The catheter passed from the right atrium to the left atrium. Mean right atrial pressure was 13 mm Hg, left atrial pressure 11 mm Hg and mean pulmonary arterial pressure 27 mm Hg. Left pulmonary venous PO_2 was 32.3 kPa but the radial arterial Pa_{O_2} was 6.24 kPa. A Greenfield inferior vena cava filter was deployed with its base at the level of the L3-L4 disc space. A bolus of tissue plasminogen activator 5 mg i.v. plus an infusion of 5 mg h^{-1} was instituted. The patient's oxygenation improved over the next 3 days and thereafter his recovery was uneventful.

Discussion

Acute RLIAS is a rare but important cause of profound hypoxia. The pathophysiology of acute RLIAS arises from an inter-atrial defect coupled with a secondary cardiac or pulmonary insult. Patent foramen ovale, which occurs in approximately 30% of the adult population,[3] is present in the majority of reported cases of acute RLIAS. ASD is present in the remainder. A rise in right atrial pressure above left atrial pressure may precipitate RLIAS. This can be the result of obstruction of pulmonary blood flow by pulmonary embolus[4] (Patient 3), increased transmural pressures in asthma,[5] right ventricular hypokinesis following right ventricular infarction[6] or coronary artery bypass grafting,[7] or as a result of elevated Pa_{CO_2} in hemidiaphragmatic paresis.[8] However, in similar cases right heart pressures can be normal, which indicates that other factors can induce RLIAS.[4 9 10] Mechanical distortion of the heart can alter the relative positions of the atrial septum and the inferior vena cava (IVC) which then directs the flow of blood from the IVC towards the inter-atrial defect and into the left atrium. Mediastinal shift following lung resection is the most commonly reported cause of RLIAS [11] Other causes of distortion of cardiac anatomy with no apparent right-to-left pressure gradient include thoracic trauma,[12] rupture of the papillary muscles,[13] after tuberculosis,[14] thoracic aortic aneurysm,[15] pericardial effusion (Patient 2),[16] and metastatic cardiac disease.[17] The mechanism of RLIAS is unclear in cases of morbid obesity,[18] cystic fibrosis,[19] adult respiratory distress syndrome[20] and exposure to low atmospheric pressure.[21,22]

Platypnoea is a sign that is strongly associated with RLIAS. This sign, first described in 1949 and given the name platypnoea in 1969, occurs in approximately one quarter of reported cases of acute RLIAS.[23,24] A corresponding postural change in oxygenation is known as orthodeoxia.[25]

RLIAS is often diagnosed unexpectedly during investigation for other causes of acute hypoxia.[26] A pulmonary angiography catheter may pass through an inter-atrial defect, as occurred in our patients, but the angiogram may be reported as normal despite the presence of a significant RLIAS.[4,13] Lung perfusion scintigraphy indicates RLIAS when early activity is detected in the brain, myocardium and kidneys.[27] It has been advocated as the investigation of choice[28] but failed to detect RLIAS in our first and second patients and in several other reported cases.[2,4,29] Injection of radiolabelled microaggregates into the arm has resulted in a normal perfusion scan whereas injection into the foot demonstrated shunt because of preferential flow from the IVC across the interatrial defect.[30]

Bubble contrast echocardiography has the greatest sensitivity for detecting RLIAS and has the advantage that it is a relatively non-invasive technique that can be performed at the bedside.[1,31,32] A syringe filled with 9 ml saline and 1 ml air is agitated, macroscopic bubbles expelled and the remaining microbubble emulsion injected i.v. The test is positive if microbubbles are seen in the left atrium (Fig. 1) within two to three cycles of the initial appearance in the right atrium.

Bubble contrast echocardiography has detected RLIAS as a first line investigation[15,22,33] and when preceding pulmonary angiogram and lung perfusion scintigram have both been falsely negative.[2,12,29] Injection of contrast via the leg may increase the sensitivity of the test as most shunting occurs via the IVC.[34] RLIAS is exacerbated when intrathoracic pressure is increased by PEEP in the artificially ventilated patient[35] and during coughing or the Valsalva manoeuvre.[31] Each of these manoeuvres can increase the likelihood of detecting RLIAS by echocardiography.

Bubble contrast echocardiography is a safe technique widely reported in the investigation of chronic RLIAS, particularly in patients who are thought to have developed paradoxical embolism.[36,37] Paradoxical embolism is not commonly associated with profound hypoxia as these patients present with systemic embolic phenomena. Patient 1 had a past history of cerebrovascular events and whether these were caused by paradoxical emboli is an interesting matter for conjecture.

Treatment of RLIAS is treatment of the underlying cause and/or closure of the PFO or ASD. Successful closure of the inter-atrial defect is frequently reported[38] although some patients have died following its closure because of right heart failure.[20,35] Temporary closure may be achieved with a balloon catheter[10] but definitive closure requires either open surgery or a percutaneous technique using an occlusive device.[6]

Patient 1 developed acute RLIAS and platypnoea. The nature of the precipitating cause remains uncertain. However, the raised perioperative pulmonary arterial pressures and the subsequent beneficial effect of nitric oxide suggests that pulmonary vasoconstriction was a contributing factor. The diagnosis of RLIAS was discounted because of the absence of a significant right-to-left pressure gradient between the atria. By the time RLIAS was diagnosed, the patient's condition precluded surgical closure of his ASD. The use of bubble contrast during the patient's first echocardiogram might have revealed the RLIAS early enough for surgery to be feasible.

Patient 2 presented with platypnoea; as this is highly indicative of RLIAS, early use of bubble contrast echocardiography was indicated. A lung perfusion scintogram failed to detect it and was falsely positive for pulmonary embolism. RLIAS was discovered during pulmonary angiography when the catheter passed through a PFO. Early use of bubble contrast echocardiography might have saved the patient from these more invasive investigations.

Patient 3 demonstrates that acute RLIAS can occur without platypnoea and without high pulmonary arterial pressures.

In conclusion, the diagnosis of acute RLIAS should be considered in any patient with unexplained acute hypoxia particularly if platypnoea or orthodeoxia is present. Neither pulmonary hypertension nor a pressure gradient between the right and left atria need be present. Bubble contrast echocardiography is more sensitive in detecting RLIAS than more invasive techniques and should be performed early.

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British Journal of Anaesthesia **85** (**6**): 926–7 (2000)

Air embolism during anaesthesia for shoulder arthroscopy

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We report a case of venous air embolism during an elective shoulder arthroscopy in which air was used as a joint distending agent. Venous air embolism was diagnosed by the sudden decrease in the end-tidal carbon dioxide concentration. The patient suffered no serious complications of venous air embolism and made a full recovery. We present this case to make surgeons and anaesthetists aware of the possibility of gas/air embolism during elective arthroscopy, when gas/air is used to distend the joint. This case also illustrates that the end-tidal carbon dioxide monitor, which is part of the standard anaesthetic monitoring system, is very sensitive in detecting venous air embolism.

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Keywords: surgery, arthroscopy; complications, air embolism; monitoring

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Venous air embolism is a known complication during anaesthesia for hip replacements, laparoscopies and operative procedures in which the operative site is above the level of the heart, as in neurosurgical and major head and neck procedures, especially in the sitting position. Although rare, venous gas embolism can occur during arthroscopy, when air or another gas is used to distend the joint. We are aware of only one report where air embolism occurred during shoulder arthroscopy. We report an additional case of air embolism during a diagnostic arthroscopy of a shoulder joint, during which the surgeon had injected 50 ml of air into the joint.

Case report

A 28-yr-old man was scheduled for elective arthroscopy of the left shoulder and subacromial decompression. He had suffered left shoulder pain for 2 yr but there was no history of trauma to the joint. Two preoperative MRI scans had not shown any abnormalities in the joint. His health status was unremarkable, apart from a history of mild asthma for which he had not taken any medication in the previous 2 yr. He had undergone an uneventful general anaesthetic in the past for inguinal hernia repair.

Anaesthesia was induced with propofol 200 mg, fentanyl 0.1 mg, and vecuronium bromide 10 mg. The trachea was intubated and ventilation of the lungs was controlled. Anaesthesia was maintained with sevoflurane and nitrous oxide in oxygen. Morphine 10 mg and ondansetron 4 mg was administered. Routine monitoring included end tidal carbon dioxide measurements. The patient was placed in the beach chair position. After a stab incision in the skin, the arthroscope with a pointed trochar was introduced into the left shoulder joint. The joint was seen using the arthroscope and 50 ml of air was injected into the joint by attaching a syringe with air to the inflow portal on the arthroscope. Within 1 min after the injection, a marked drecrease in the end tidal carbon dioxide ($E\text{T}_{\text{CO}_2}$) from 4.0 to 1.5 kPa was noted. The electrocardiogram showed a 1-mm rise in the ST segment, and the heart rate increased from 56 to 90 beats min^{-1}. There were no changes either in the oxygen saturation or in the non-invasive blood pressure. An air embolism was suspected and the patient was placed horizontal and nitrous oxide discontinued. The end tidal carbon dioxide concentration returned to 4.0 kPa after 4 min. The surgical procedure was allowed to continue after ensuring the condition of the patient was stable and the $E\text{T}_{\text{CO}_2}$ concentration had returned to normal. There was an episode of bradycardia 15 min following the incident during which the heart rate decreased to 38 beats min^{-1}. This responded to 0.6 mg of i.v. atropine.

The patient made a full recovery from the anaesthetic at the end of the procedure, without any sequelae. He remained stable for the next 48 h and was discharged home.

Discussion

Venous air embolism may occur during any operative procedure in which the operative site is above the level of the heart and non-collapsible veins are exposed to atmospheric pressure, or when air or any other gas is introduced under pressure into a body cavity. The clinical presentation and complications of venous air embolism depend on the dose and the speed of air entry into the vein and the filtering capacity of the lungs.

Although venous air embolism of some degree is detected in all patients undergoing neurosurgical procedures in the sitting position,[1] it is very rare in shoulder arthroscopy. Air

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and other gases have been used to distend the joint in arthroscopy since 1921. Fatal pulmonary air embolism has been reported during arthroscopy of injured knee joints.[2 3] It is presumed that air entered the circulation through the exposed venous sinuses in these cases. We are aware of only one case of venous air embolism during a shoulder arthroscopy.[4] There are, however, theoretical risks of embolism during this procedure. In the beach chair position, used for shoulder operations, the operative site is higher than the right atrium. In addition, during arthroscopy the pressure inside the joint may be 5–10 times higher than the venous pressure and if a vein is punctured during insertion of the arthroscope, any agent used to distend the joint may enter the venous system.

Because of the low morbidity and anaesthetic complication rate associated with shoulder arthroscopy, the procedure is performed as a day case in most hospitals. Air is commonly used as the joint distending agent because of the better view obtained, when compared with normal saline.

The possible mechanisms of developing a venous air embolism during arthroscopy are: injection of air into an injured joint, where the air can get into the exposed venous sinuses because the intra-articular pressure during arthroscopy is high and may reach peak values of 300 mm Hg with sudden manipulation of the joint;[5] or accidental injection of air into a vein in the joint.

In our case there was no history of trauma, preoperative MRI scans showed no abnormalities in the joint and arthroscopy did not show any disruption in the joint surface. It is presumed that a vein was accidentally punctured during the stab incision or by the introduction of the arthroscope into the joint. The raised intra-articular pressure because of the injected air and the manipulation of the joint resulted in air entering an open vein.

There are several reports in the anaesthetic literature where the use of sophisticated monitors to detect venous air embolism early in operations, with a high risk of development of venous air embolism, has resulted in a significant reduction in morbidity and mortality.

Transoesophageal echocardiography is the most sensitive monitor for early detection of venous air embolism (detects as little as 0.02 ml kg^{-1} of air).[6] Others include pulmonary artery catheters, pre-cordial Doppler probe and $E\mathrm{T}_{\mathrm{CO}_2}$ and nitrogen measurements.

For day case arthroscopies an inexpensive, non-invasive, sensitive and easy-to-use monitor is essential. The pre-cordial Doppler probe meets the above criteria. It is very sensitive, but picks up interference from other sources. Before it becomes a useful tool for early detection of venous air embolism, familiarity with its use is essential. In most district general hospitals, however, capnography remains the main monitor for the early diagnosis of venous air embolism. It has fewer sources of interference than echocardiography and pre-cordial Doppler. It is widely used and is sensitive (sensitivity of 0.4 ml kg min^{-1}),[7] but is non-specific for air embolism. Above all, awareness of the possibility of air embolism, a high index of suspicion and vigilance are most important in arthroscopy when air or other gases are used to distend the joint. Early detection of venous air embolism will allow for prompt treatment before serious clinical complications develop.

A significant venous air embolism will manifest as bronchospasm, hypoxaemia, hypercapnia, decreased $E\mathrm{T}_{\mathrm{CO}_2}$, hypotension, cardiac dysrhythmias and cardiovascular collapse, depending on the size of the embolus and the rate of entry of air into the veins.

Management of clinical venous air embolism includes measures to prevent expansion of the embolus and further entry of air into the venous system. The operative site should be lowered below the level of the heart, if possible and flooded with fluids while haemostasis is obtained. Nitrous oxide should be discontinued and oxygen increased to 100%. Blood pressure and central venous pressure should be supported with fluids, vasopressors and inotropes If a large amount of air is entrained, the left lateral decubitus position may improve right ventricular outflow. Further treatment includes insertion of right atrial catheter and aspiration of air from the right side of the heart. In the event of cardiovascular collapse, cardiovascular resuscitation should be commenced.

Prevention is the key to the management of venous air embolism. Patients at risk should be well hydrated in order to reduce the pressure gradient between the surgical site and the right atrium. Surgical haemostasis is essential at all times. Intravenous air is five times more dangerous than carbon dioxide.[8] Therefore, carbon dioxide or normal saline are safer agents for distension of joints during arthroscopy.

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BJA

HISTORY

The inventions of John Blease

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Though he had no formal training in engineering, John Blease of Merseyside invented numerous devices that greatly benefited the practice of anaesthesia. Starting with the turning of component parts for simple anaesthetic machines in the 1930s, he was introduced to clinical anaesthesia and became skilled in the art of dental anaesthesia. In the early 1940s he developed the all-purpose Alfo-Blease anaesthetic machine. In 1945 he designed an intermittent positive pressure ventilator, which was used successfully around Liverpool. After World War II he improved this into the Blease 'Pulmoflator', which was the first British positive-pressure ventilator in commercial production. From then until the early 1960s he patented many other inventions, duly utilized in the manufacture of anaesthetic equipment, in which industry the Blease name survives in the company he founded.

Br J Anaesth, 2000; **85**; 928–35

Keywords: history, anaesthesia; history, Blease, John Henry; equipment, anaesthesia machines; equipment, ventilators

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Between 1939 and 1960 John Henry Blease successfully applied for no less than 19 patents for anaesthetic equipment which he invented. Thereafter, he was involved in several more patents for inventions by Roger Manley, who had received his advice and support.

Early days

John Blease was born in 1906 in Bootle and grew up in Moreton on the Wirral (Merseyside). Although he began work as a butcher's boy at 14 yr of age, he had a mechanical mind and was brilliant at repairing clocks. Next he applied himself to tractor repairs, then became a motorcycle enthusiast, and in his late teens set up a car repair business jointly with a younger brother. In the early 1930s he built his own 1000 cc motorcycle, which he called the 'Blease Special' (Fig. 1). With this he entered races on sand against prestige machines and for 6 yr, beginning in 1933, he won every race in which he competed at Wallasey and Southport (personal communication, Tony and Doreen Blease).

Anaesthetic machines

At this time John Blease befriended a neighbour, Dr Henry Roberts, who was a general medical practitioner and anaesthetist to the Liverpool Dental Hospital.[1] At Roberts' request, Blease made component parts from drawings of American (Gwathmey and Heidbrink) anaesthetic machines. His work impressed a full-time anaesthetist, Dr John Halton, with whom Blease also became friendly. Through these two men, Blease became acquainted with clinical anaesthesia. The improved Roberts dental anaesthetic machine (Fig. 2) became very popular and is said to have been installed in the Cunard-White Star liner *Queen Mary*. In 1937 Roberts died suddenly[1] and his role as dental anaesthetist was taken on by Blease(!), who became highly skilled in the art. Furthermore, Blease established contact with the Liverpool surgical instrument company, Alexander and Fowler. In 1938, Blease and George Fowler applied for a patent for improvements in anaesthetic apparatus[2] making use of manifold technology, valves and temperature compensation. They filed a second patent application in 1940[3] for the addition of carbon dioxide absorption and one-way valves. Utilization of these advances resulted in the Alfo-Blease anaesthetic machine, which was described in R. J. Minnitt's revision of the *Handbook of Anaesthetics* (5th edition, 1940).[4] Blease filed two more patents for improvements in 1941[5] and 1942;[6] the latter invention was a flowmeter with a by-pass: it avoided erratic readings and allowed for a more open scale. Again these patents were incorporated in an improved model of the Alfo-Blease

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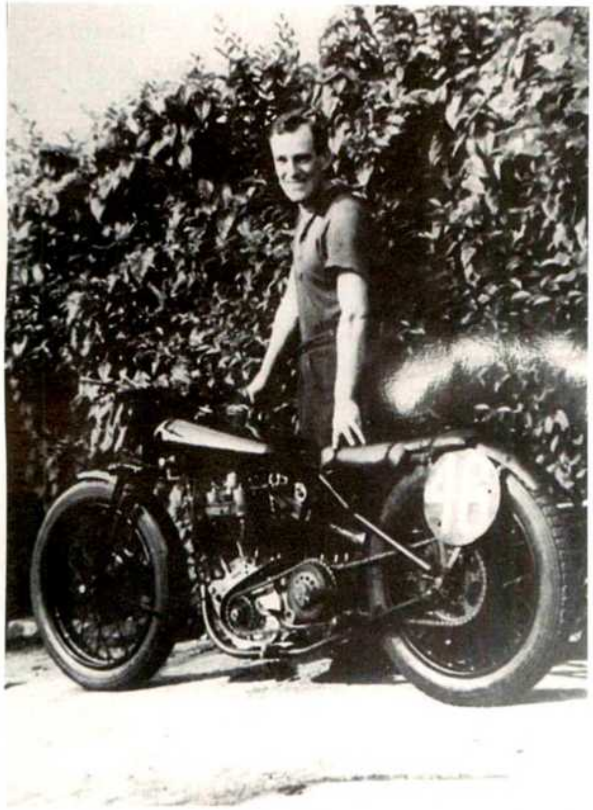

Fig 1 John Blease and the 'Blease Special' (courtesy of Mr M. A. Blease).

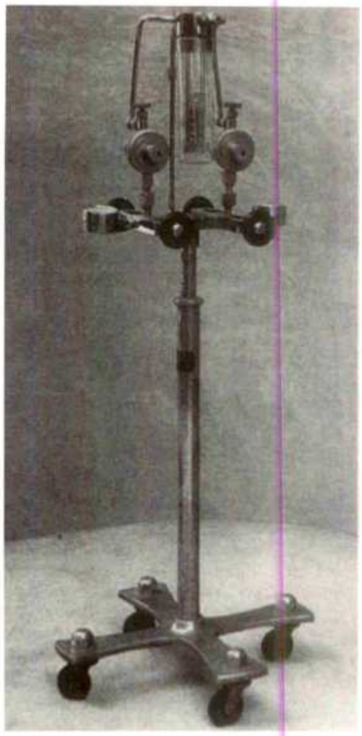

Fig 2 Roberts dental anaesthetic machine (courtesy of Mr M. A. Blease).

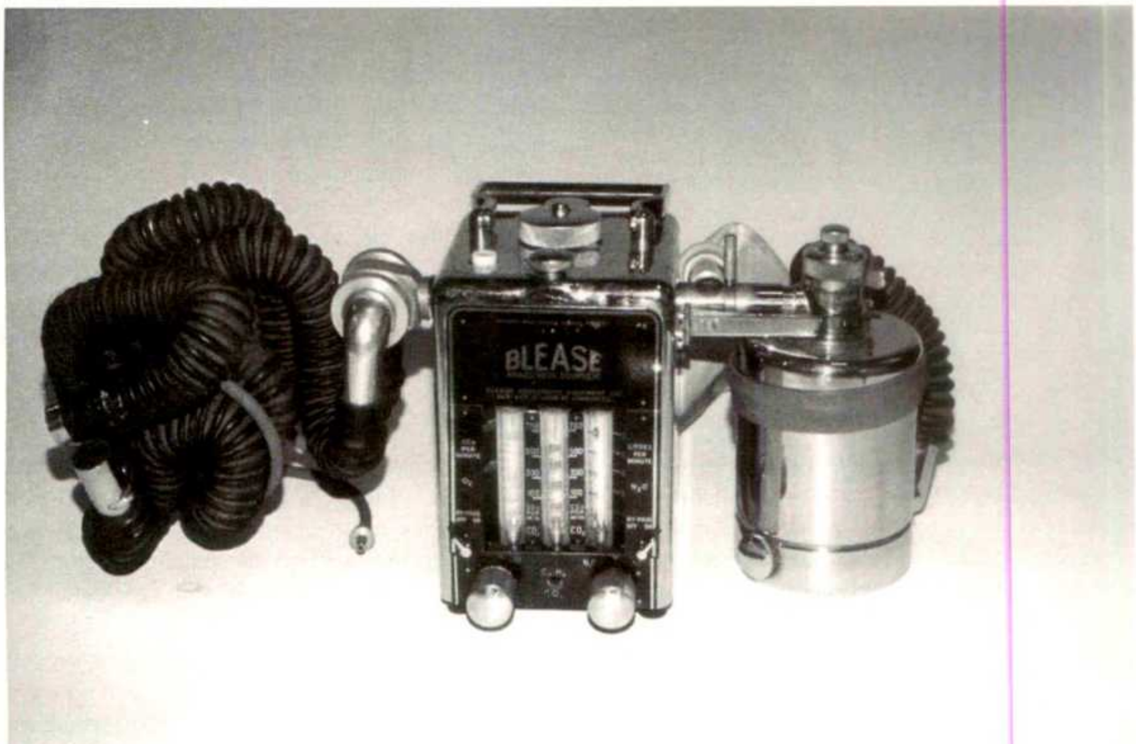

Fig 3 Alfo-Blease anaesthetic machine, circa 1948. Prior to this, the head bore the insignia 'Alfo-Blease' (© Thackray Medical Museum, 2000).

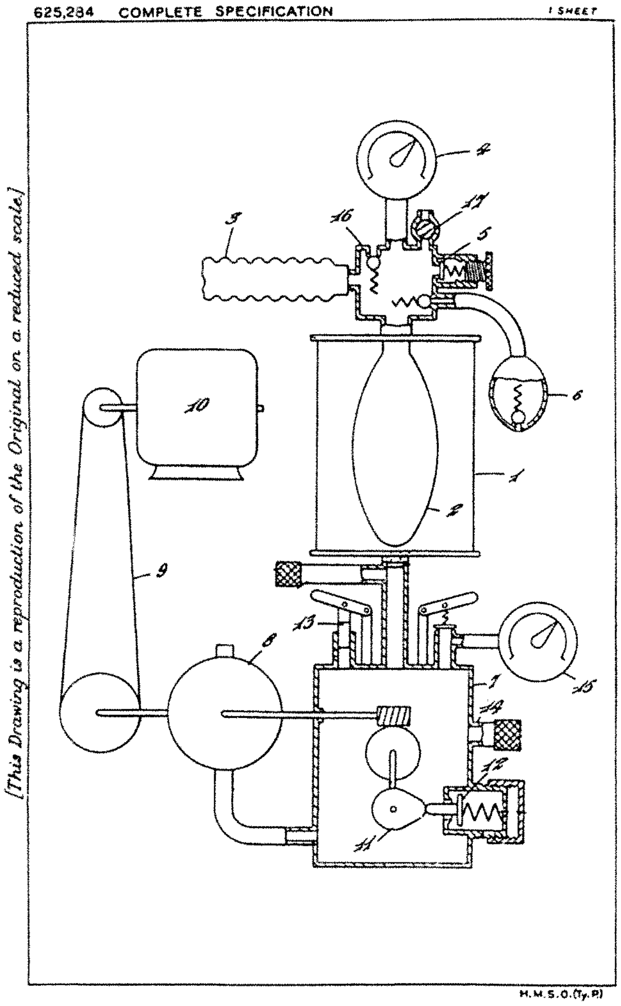
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Fig 4 Drawing of prototype of Blease 'Pulmoflator', 1947 (modified from British Patent 625,284). Key: 1, glass cylinder; 2, rubber rebreathing bag; 3, corrugated tubing to anaesthetic apparatus; 4, inflation pressure gauge; 5, adjustable expiratory valve (semi-closed circuit); 6, hand bellows (closed circuit); 7, compression chamber; 8, rotary pump with air inlet; 9, belt gearing; 10, electric motor; 11, cam; 12, adjustable deflation valve (cam operated); 13, manual valve to discontinue pressure; 14, branch for introduction of oxygen, nitrous oxide; 15, inflation pressure gauge; 16, inspiratory valve; 17, auxiliary inlet to enable introduction of oxygen or carbon dioxide. *Modus operandi* The 'bag in a bottle' is rhythmically squeezed by the electric compressor through the cam and valve mechanism.

machine (Fig. 3). This portable apparatus included a head (rectangular metal box 6.5 in. deep ×5 in. × 4.5 in.), a soda-lime cannister, a rebreathing bag and afferent and efferent corrugated tubes attached to an 'E' mount (with two non-return valves) for connection to the face-mask or tracheal tube. The head had three rotameters calibrated for oxygen, nitrous oxide and cyclopropane. Inside the box was an ether vaporiser with a 3-way tap and control valve, enabling the gases to either pass over or bubble through the ether.[7 8] The 'all purpose Alfo-Blease' was well received and by 1944 Alexander and Fowler Ltd were producing 100 machines a year (price £100 each).[9]

Intermittent positive pressure ventilators

In the early 1940s, during the World War II bombing of Liverpool, Blease was pressed into further anaesthetic service and was appointed 'Emergency Anaesthetist' at Birkenhead General Hospital. He even anaesthetised thoracic cases for Mr Hugh Morriston-Davies (pioneer of thoracoplasty in the UK).[10] This was an astonishing achievement on two counts: first, anaesthesia in Britain was traditionally administered by physicians and, secondly, Mr Morriston-Davies would not have tolerated a 'second best' anaesthetic. 'Controlled ventilation' had been introduced into British anaesthesia in 1941[11] and thoracic anaesthetists became 'bag squeezers' when the chest was opened. Blease had plenty of time to reflect on the drudgery of manually controlled ventilation, and in 1945 he designed a pulmonary ventilator, which, with the help of Dr J. Halton, was tested successfully on patients.[12] This apparatus was much appreciated when the use of d-tubocurarine in anaesthesia became more common and necessitated controlled ventilation throughout many surgical operations.[13]

In 1945, after World War II, Blease left the Wirral (and Alexander and Fowler) to join Multitone Electric Co Ltd, which made hearing aids, at 223–227 St John Street, London (personal communication, Tony and Doreen Blease). From this location Blease continued to supply the 'Alfo-Blease', imprinted with the name 'Blease Anaesthetic Equipment Co. Ltd'. From 1946 until his retirement he resided at Royston Park Road, Hatch End, Middlesex where, in a large workshop, he did most of his inventing. In 1946 he applied for a patent for a portable mechanical ventilator,[14] shown diagrammatically in Fig. 4. This was the original prototype of the Blease 'Pulmoflator' which operated on the 'bag in a bottle' principle. The driving air came from the compressor side of a rotary vacuum pump, belt-driven by an electric motor. Blease chose to purchase this, because it was smaller and cheaper than a designated compressor. The remainder of the apparatus was Blease's invention. Within the compression chamber a blow-off valve was operated by a cam, connected by worm-gearing to the rotary pump. Adjustable spring-loaded valves controlled the minimum and maximum pressures. The frequency of cycling (respiration) was controlled by the speed of the motor, while the inspiratory: expiratory ratio was controlled by the characteristics of the cam—the disadvantage being that these were independent of pulmonary pressures. The cam and valve mechanism clearly came from car technology.

Blease lodged another patent in 1948[15] (pressure pre-set ventilator) whereby the prototype was improved (Fig. 5). The cycling mechanism was changed to a spring and ratchet device (Fig. 6) reminiscent of motorcycle technology. Only one model of this early 'Pulmoflator' was built. To facilitate easy transport by motorcar it was made in two parts: the

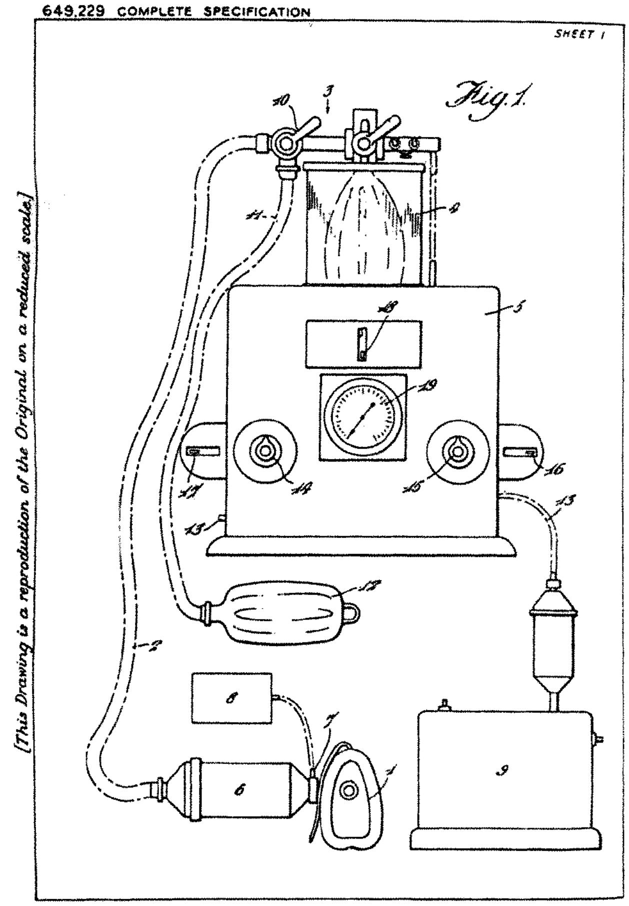
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Fig 5 Drawing of early Blease 'Pulmoflator', 1949 (modified from British Patent 649,229). Key: 1, face-mask; 2, flexible tubing; 3, valved head; 4, air chamber; 5, casing, housing the operating mechanism; 6, carbon dioxide absorber (soda-lime); 7, pipe for introduction of anaesthetic gas from source; 8, source; 9, pump for supplying air through tubing 13, to another air chamber (within 5, separated by a flexible diaphragm from a vacuum chamber); 10, manually controlled valve to disconnect tubing 2 from head 3 and connect 2 to tubing 11 leading to rubber bag 12 for manual respiration; 14, knob to control needle valve for adjusting inspiratory time; 15, knob to control needle valve for adjusting expiratory time; 16, control lever for compression spring (resisting the diaphragm), which regulates inflation pressure; 17, control lever for slide valve to hold lungs inflated; 18, lever for manual control of respiration; 19, pressure gauge. *Modus operandi* The 'bag in a bottle' is rhythmically squeezed by the electric compressor through the 'cycling box', which is a spring-diaphragm-ratchet device explained in Fig. 6.

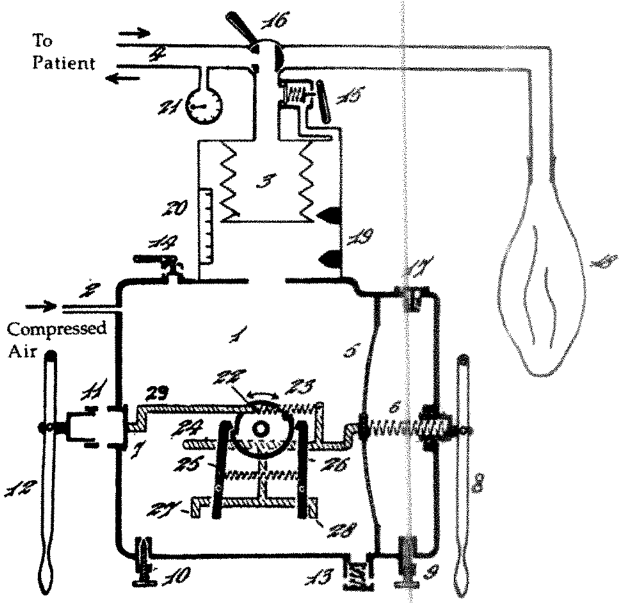

Fig 6 Drawing of New Blease 'Pulmoflator' (P.1), 1952. Key: 1, pressure chamber; 2, compressed air inlet; 3, concertina reservoir bag; 4, tubing to patient; 5, flexible diaphragm; 6, compression spring within vacuum chamber; 7, exhaust valve; 8, control lever for cycling pressure; 9, needle valve controlling duration of expiratory phase; 10, needle valve controlling rate of inflation; 11, slide valve to hold lungs inflated; 12, control lever for 11; 13, positive pressure safety valve; 14, valve to allow spontaneous breathing (inactivating ventilator); 15, adjustable spring-loaded spill valve; 16, 'manual/auto' control; 17, one-way valve; 18, breathing bag (for manual ventilation); 19, pointers; 20, calibrated scale; 21, manometer; 22, notched disc; 23, compression/expansion spring; 24, activating rod; 25 and 26, ratchet bars; 27 and 28, striking pins; 29, connecting rod. *Modus operandi* Compressed air enters the main chamber and acts on the outside of the concertina bellows, the contents of which therefore inflate the patient's lungs. During this phase the diaphragm is displaced to the right and the notched disc rotates clockwise. At the crucial point the ratchet mechanism flicks over, opening the exhaust valve so that the pressure in the main chamber falls to atmospheric and expiration occurs. The spring pressing on the diaphragm causes it to move in the opposite direction until the ratchet flicks over again, closing the valve and restarting the inspiratory phase.

'bag in bottle' with a 'Blease 1 cycling box' being the first part, and the belt driven vacuum pump the second. In 1950, Dr H. J. V. Morton (an anaesthetist at Hillingdon Hospital, Uxbridge) used it to perform controlled ventilation of patients undergoing hernia repair. He recorded pneumographs and showed that the machine could produce a respiratory pattern very close to 'normal', i.e. spontaneous respiration, under cyclopropane anaesthesia.[16]

The 'new Blease Pulmoflator' (P.1) launched about the end of 1950 was the first ventilator freely available commercially in Britain. The basic workings were as described above, but the 'bag in a bottle' was replaced by concertina bellows in a perspex cylinder (initially not antistatic)—included in another patent applied for by Blease in 1951.[17] Measurement of the tidal volume was facilitated by adjustable pointers and a calibrated scale arranged outside the perspex cylinder (Fig. 6). The clinical use of this ventilator was described in 1952.[18] By 1953, driven by the need for vacuum pumps, Blease left Multitone Electric Co. and joined Edwards High Vacuum (now Edwards BOC). Operating from 12 Hinde Street, London W1, he was able to manufacture many 'Pulmoflators' (P.1): about three or four a month, all made one at a time! It is estimated that, over 5 yr, a total of 200 were produced; no serial numbers were issued (personal communication, Tony and Doreen Blease). In 1953, he incorporated the P.1 into a self-contained anaesthetic machine (the 'combined pulmoflator', P.2). This included rotameters (for oxygen, nitrous oxide, cyclopropane and carbon dioxide), racks

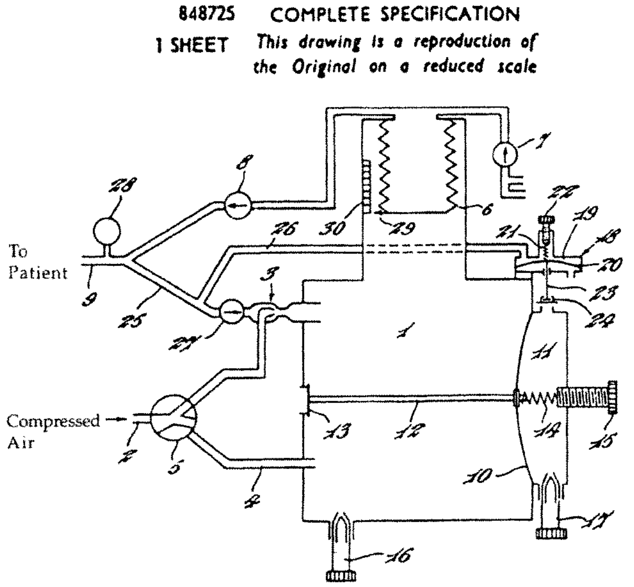
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Fig 7 Drawing of triggering device, 1959 (modified from British Patent 848,725). Key: 1 air chamber; 3 Venturi-effect device; 5 two-way differential valve; 6 collapsible bellows; 7, 8 one-way valves; 9 pipe to patient; 10 diaphragm; 11 low-pressure chamber; 12 rod with valves 13; 14 spring with regulator 15; 16, 17 adjustable bleed valves; 18 triggering mechanism comprising chamber 19 with bowed diaphragm 20, spring-loaded by spring 21 with regulator 22; 23 rod; 24 non-return valve; 25 pipe, leading from patient connection through a one-way valve 27 to the Venturi-effect device 3, which operates to apply a partial vacuum to the patient's lungs; 26 pipe leading from 25 to the chamber 19 of the triggering mechanism; 28 pressure gauge; 29 pointer, which moves over a scale 30, to indicate the degree of deflation of bellows 6 (i.e. tidal volume). *Modus operandi* If the patient attempts to breathe, the slight negative pressure in the breathing system lifts the diaphragm 20, opening the valve 24 and admitting air to the low pressure chamber 11. Thereupon the diaphragm 10 moves quickly to the left, closing valve 13. As a result the pressure in the air chamber 1 builds up, squeezing the contents of the bellows into the patient's lungs.

for gas cylinders, blood pressure apparatus, suction apparatus, bronchoscope fittings, instrument trays and a metal water container.

Other devices of use in anaesthesia

John Blease applied his mind to several other aspects of anaesthesia. In November 1948 he registered another two inventions at the Patent Office, London. These were an improved assembly for tracheal tubes[19] and interchangeable apparatus for varying the proportion of gas flow through carbon dioxide absorbing material.[20] In November and December 1950 he registered two more inventions! The first of these was a hypodermic needle with a securing transverse plate and an inclined external end for easy attachment of either a diaphragm cap or a syringe;[21] the second was a double-cuffed tracheal tube.[22] In 1953 he invented a device for controlling the flow of iv fluid through resilient tubing.[23] Stimulated by the 1952 poliomyelitis epidemic in Copenhagen he designed a manual resuscitator, incorporating a non-return valve with no resistance to expiration. This was reviewed in 1954.[24]

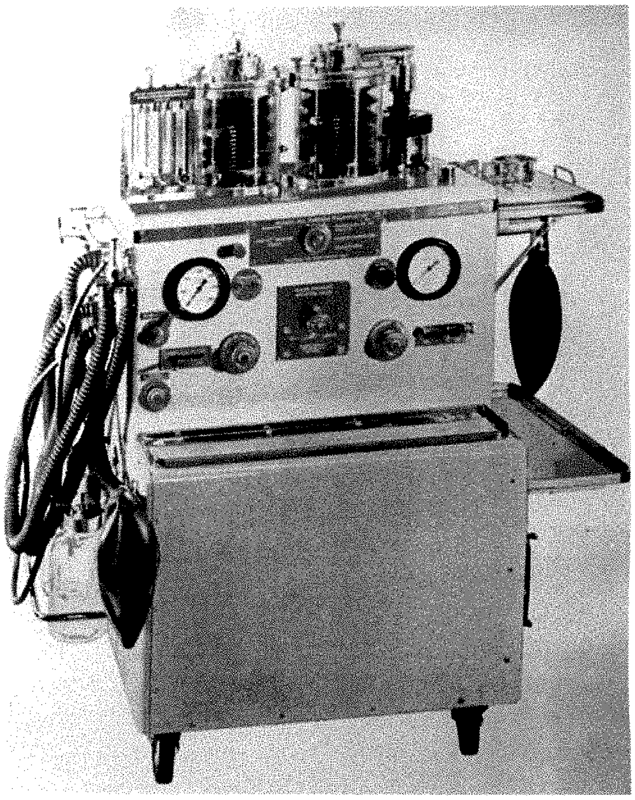

Fig 8 Blease 'Pulmoflator' Model P11 (courtesy of Mr MA Blease).

Improvements in pulmonary ventilation

Next John Blease looked again at respiration. In 1953 he designed an improved control valve for use in either an anaesthetic machine or portable resuscitation apparatus.[25] In 1957, Blease moved his company to Ryefield Crescent, Northwood Hills, Middlesex where, in bigger premises, he expanded the manufacture of 'Pulmoflators'. The same year he lodged a patent for a triggering device (Fig. 7).[26] This was utilized in model P.3 which also had an injector, providing variable negative pressure during the expiratory phase.[27] The P.3 was designed only for 'open circuit' and was intended for short or long term use in cases of respiratory paralysis/insufficiency. Next, model P.4 was designed for anaesthetic use only with a 'closed or semi-closed circuit'. The injector was modified so that variable degrees of negative or positive pressure during expiration were possible.[27] A combined ventilator/anaesthetic apparatus (model P.5) was also produced. Model P.6 of the 'Pulmoflator' incorporated a gauze-covered air 'intake', i.e. filter, so that in addition to anaesthesia, the ventilator could be used for emergency treatment of respiratory insufficiency in a hospital ward. Designed only for 'open circuit' it was also combined with anaesthetic apparatus—model P.7. In 1959 these 'Pulmoflators' were functionally

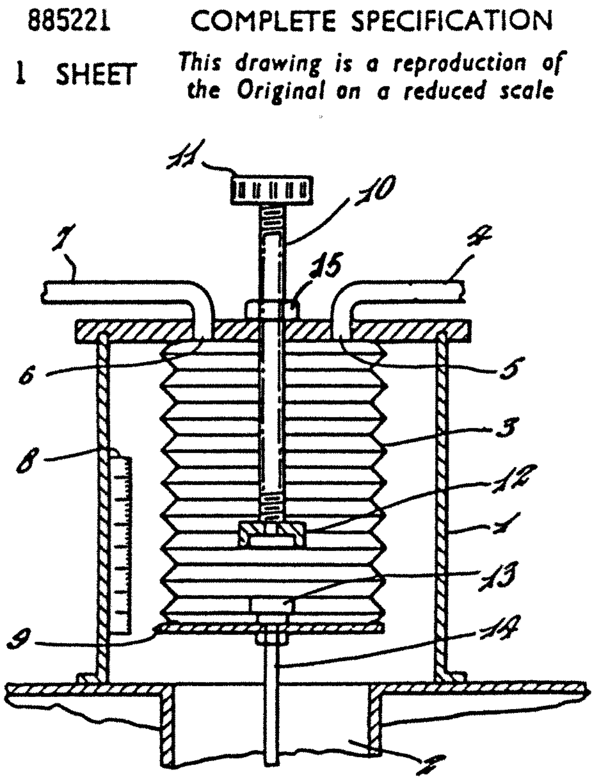
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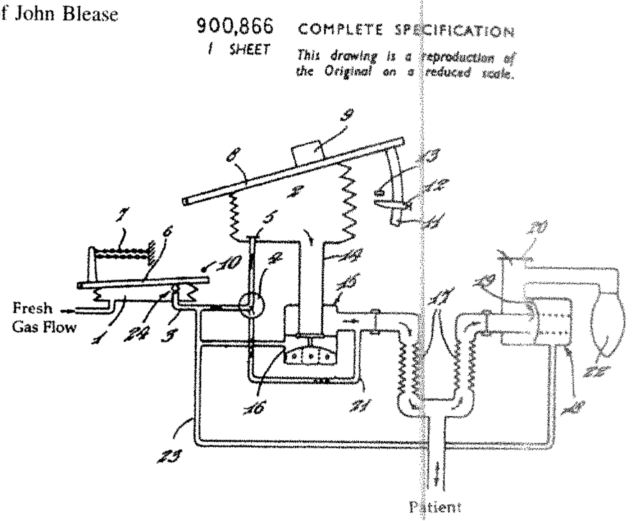
Fig 9 Drawing of apparatus for constant volume ventilation, 1959 (modified from British Patent 885,221). Key: 1, transparent chamber which is cyclically pressurized and vented to atmosphere through opening 2, (by pressure-operated valve mechanism); 3, collapsible bellows; 4, inlet pipe for admission of air or gases; 5, inlet port; 6, outlet port; 7, outlet pipe to patient; 8, scale with pointer 9 for indication of tidal volume; 10, threaded rod with knob 11 at its upper end and a stop 12 at its lower end, arranged to co-operate with an abutment 13; 14, depending rod; 15, lock nut. *Modus operandi* Adjustment of 10–15 facilitates presetting the stroke of the bellows.

analysed[27]—all were constant flow generators in inspiration, with pressure cycling of inspiration-expiration and time cycling of expiration-inspiration. In the expiratory phase all were pressure generators: P.1 atmospheric followed by positive pressure, P.3 constant negative pressure, P.4 and P.6 having negative and positive pressure components.

By 1960 the Blease 'Pulmoflator' model P.10 was commercially available. It incorporated a large two-way valve for selection of either 'open circuit' or 'closed circuit', and had two concertina bellows units. This 'all-purpose' ventilator was also combined with anaesthetic apparatus—model P.11 (Fig. 8). In 'closed circuit' this machine operated as a P.5, and in 'open circuit' as a P.7. Another patent, which Blease had lodged in 1957 for a constant volume ventilator[28] (Fig 9) was utilized by 1960 in 'Pulmoflator' models P.3—P.11. In reality this was a bellows stroke-limiting 'stop', which enabled tidal volume to be preset. In the successive models of 'Pulmoflator' the basic workings were the same: each new invention was simply added on.


900,866 COMPLETE SPECIFICATION
1 SHEET
This drawing is a reproduction of the Original on a reduced scale.
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Fresh Gas Flow
1
24
3
16
21
22
18
23
Patient

Fig 10 Drawing of prototype of Manley ventilator, 1960 (modified from British Patent 900,866). Key: 1, bellows, connected to a source of gases under pressure, and in communication with a 2nd bellows 2 through tube 3 containing a two-way tap 4; 5, valve (V1); 6, pivoted frame, biassed by means of tension spring 7; 8, pivoted frame, adjustably biassed by a movable jockey weight 9; 10, movable contact coupled to valve 5 (V1); 11, arcuate arm, having adjustable stop member 12; 13, contact, coupled to valve 5 (V1); 14, wide bore tube leading from bellows 2 to inhalation valve 15 (V2) attached to 16 spring biased diaphragm in small pressure chamber; 17, flexible tubing to patient; 18, exhalation valve (V3) attached to 19 spring biased diaphragm in small pressure chamber; 20, expiratory valve; 21, by-pass tube from two-way tap 4 to facilitate manual respiration; 22, breathing bag; 23, tube, pneumatically linking valves V1, V2 and V3; 24 valve (needle and seating) which closes when bellows 1 is empty, providing a constant back pressure on the rotameters. *Modus operandi*: Inspiration; pressure generator (from weighted bellows 2). Bellows 1 fills during this phase. Inspiratory-expiratory cycling; time cycled by the filling of bellows 1 until contact 10 trips a toggle and lever (bistable) system and valve 5 (V1) opens. Due to the pneumatic linking 23, this causes valve 15 (V2) to close and valve 18 (V3) to open. Expiration; passive pressure generation to atmosphere. Bellows 1 empties and bellows 2 fills during this phase. Expiratory-inspiratory cycling; volume cycled by the setting of 12, so that when bellows 2 has filled to the set volume, contact 13 trips the toggle and lever (bistable) system in the other direction—valve 5 (V1) closes, valve 15 (V2) opens and valve 18 (V3) closes.

The Manley ventilator

In July 1960, Blease Anaesthetic Equipment Ltd filed a patent application for a new mechanical ventilator designed by Roger E. W. Manley.[29] This machine incorporated two bellows in communication with each other (Fig. 10). Simultaneously, a second patent application was filed for a combination of two valves designed to improve the performance of the new ventilator.[30] At that time Roger Manley was a Senior House Officer at Westminster Hospital, who had been impressed by the need for a simple, reliable and inexpensive ventilator. Using various parts including the bellows from a Blease 'Pulmoflator', he had assembled in the garage of his home a working model of a ventilator, powered by the fresh gases from the anaesthetic machine. Encouraged by Dr Geoffrey S. W. Organe and other anaesthetic staff at Westminster Hospital, Manley had then taken his prototype to John Blease, who agreed to develop and market it. In his paper 'A new mechanical

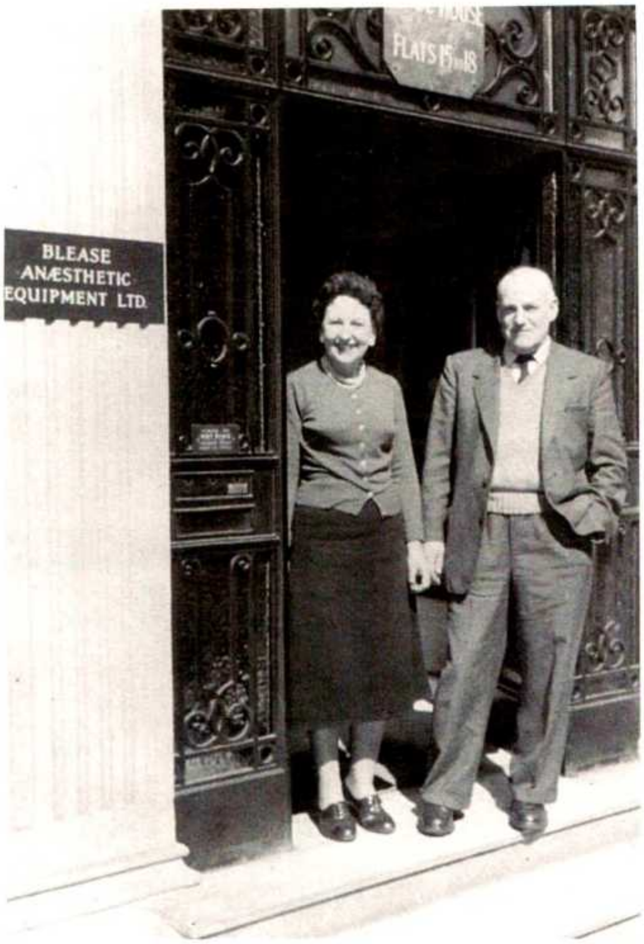

Fig 11 Mr and Mrs J. H. Blease, London, 1955 (© Leslie Rendell-Baker, 1955).

ventilator' published in *Anaesthesia* in 1961,[31] Manley thanked John Blease 'for his continued help in developing the production model of the ventilator'. The Blease–Manley ventilator (minute volume divider) was an immediate and lasting success, many models being still in use around the world.

Retirement

In his commercial endeavours John Blease was supported by his wife, Doreen, who was Company Secretary for many years (Fig. 11); his son Tony demonstrated and serviced 'Pulmoflators' all over the world. Perhaps not surprisingly, Roger Manley also joined the firm. John Blease decided for health reasons to retire in 1964. The Company was sold in 1965 and in 1966 moved to Deansway, Chesham, Buckinghamshire (the present address of Blease Medical Equipment Ltd). Blease remained active in retirement. In 1983, his achievements were recognised by the Liverpool Society of Anaesthetists, which elected him an Honorary Member. He died in 1985 at the age of 79 yrs.[10] Modern anaesthesia owes much to his legacy of inventions!

Acknowledgements

I thank Mr Tony Blease and the late Mrs Doreen Blease for their help and cooperation as well as two illustrations. Original drawings of John Blease's patented inventions were obtained from the national patent collection in the British Library, London, which is open to the public; permission to reproduce these drawings was kindly given by Tony Blease and Blease Medical Equipment Ltd. I thank the Thackray Medical Museum and Prof. Leslie Rendell-Baker for each providing an illustration.

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British Journal of Anaesthesia **85 (6)**: 936–42 (2000)

Correspondence

Serum S100 protein as a marker of cerebral damage during cardiac surgery

Editor,–We read with interest the review by Shaaban Ali and colleagues regarding serum S100 protein as a marker of cerebral damage during cardiac surgery.[1] We agree with the authors that S100 protein is a potentially useful marker of central nervous system (CNS) injury in many settings, including head injury, acute stroke and subarachnoid haemorrhage. Our group has previously demonstrated that increased levels of S100 protein may be related to unfavourable outcomes in the setting of severe head injury.[2]

However, we wish to highlight an important caveat that was poorly addressed by the review. While conventional wisdom suggests that S100 protein is exclusively derived from glial cells in the CNS, there is increasing concern that extracerebral sources may significantly contribute to blood levels of the marker in the setting of cardiac surgery.[3] Jönsson and colleagues[4] discovered a significant amount of S100 reactivity both in blood from the surgical field and in shed mediastinal blood from patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). They also found that these elevations of S100 were significantly decreased after washing with a cell-saving device. Westaby and colleagues[5] evaluated whether perioperative release of S100 protein after CABG operations with CPB could predict early or late neuropsychological impairment. To exclude non-cerebral sources of S100 protein, they did not use cardiotomy suction or transfuse shed mediastinal blood. They showed no significant correlation between S100 protein release and neuropsychological measures 5 days or 3 months after surgery.

Further evidence relating the process of CPB to S100 elevation is provided by Anderson and colleagues,[6] who compared the levels of S100 protein after CABG with and without CPB, and found a 10-fold greater increase in S100 protein in CABG with CPB than off-pump grafting. The same authors also demonstrated that not using the cardiotomy suction during CABG with CPB resulted in a six-fold reduction in the serum S100 protein levels seen after conventional CABG with cardiotomy suction. These data imply that a substantial proportion, and possibly most of the serum S100 elevation observed after CPB with cardiotomy suction, may be of extracerebral origin.

It is not known whether the 'S100' detected in these studies is actually S100 or another protein, which cross-reacts with the antibody used in these assays. Whatever the cause of these findings, we would echo the views expressed by Anderson and colleagues,[7] who suggest that until methodological problems are solved, S100 protein should be used with caution as a serum marker of brain damage after operations that involve CPB, and that cardiotomy suction should be absolutely avoided in future studies that relate S100 release to neurological outcome. An alternative is to use sampling techniques that better localize S100 release to the cerebrovascular bed.[2] S100 protein may well be a sensitive marker of cerebral injury, but at least in the setting of cardiac surgery, it is not a highly specific one.

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Editor,–We are pleased with the interest shown in our review by Kuzumi and colleagues.[1] After our review was accepted for publication, concerns were raised about extracerebral sources of S100 β protein, mainly during, and up to 5 h after cardiopulmonary bypass (CPB)[2,3] the so-called early S100 release pattern.[1] However, the biological half-life of S100 β protein has recently been identified as less than 1 h.[2] Therefore, if cardiotomy suction or autotransfusion are in use during cardiac surgery appropriate sampling times should be selected (~2 h after suction or autotransfusion).

Jönsson and colleagues,[2] after correction for extracerebral contamination by a kinetic model, measured S100 β protein levels in the first 4 h after CPB and they were found to correlate with the results of subsequent neuropsychological testing. These findings support the importance of using early S100 β protein values in evaluation of cerebral function and indirectly suggest a cerebral origin of the early S100 β protein. However, the inability to establish a consistent correlation between S100 β protein elevation and abnormal neuropsychological performance after CPB[4] may be because abnormal neurophysical performance is primarily related to defects in grey matter,[5] whereas white matter alterations seem to be responsible for elevations of S100 β protein.[6] It may, therefore, be difficult to correlate these two measures of brain injury postoperatively although the two may be complementary.[6]

Moreover, a secondary or late release pattern of S100 β protein (15–48 h)[1] in the postoperative period is a sign of further neurological injury,[7–9] unless there is ongoing autotransfusion from chest tubes. Georgiadis and coworkers found that S100 β protein levels at 24 h after CPB surgery have a specificity and sensitivity of approximately 90% in identifying patients with cerebral injury. On the other hand, S100 β protein levels of less than 1.1 μg litre^{-1} on the first postoperative day had a specificity of 97.4% in excluding patients without cerebral injury.[9] This study[9] supports the importance of the late release pattern of S100 β protein in early detection of brain injury after CPB.

The introduction of a rapid whole blood S100 β protein assay[10]

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and with proper identification of extracerebral sources of S100 β protein will help in the better understanding of the clinical significance of its release during and soon after CPB.

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HIV exposure risk and management

Editor,–Diprose and colleagues' study of anaesthetists' knowledge of HIV exposure risk and management of post exposure prophylaxis in Southampton,[1] is an important piece of work. We have done an identical survey in our academic department in Cape Town, where the antenatal population prevalence of HIV is 7.1% (Western Cape Department of Health, personal communication).

With Diprose and colleagues' permission, we used an identical questionnaire. Due to delay in the availability of the *BJA*, we could ensure that no members had prior access to the paper. The Groote Schuur Hospital (GSH) Department of Anaesthesia is similar in size to the Southampton General Hospital (SGH) Department, consisting of 25 consultants and 40 registrars. We had a response rate of 97% (63 of 65 anaesthetists in the department).

Questions, correct answers and results are shown below:

1. What is the rate of HIV transmission after a contaminated needlestick injury?
Answer: 3 per 1000 injuries (Correct from 1 per 1000 to 9 per 1000)
GSH 73% correct SGH 34% correct

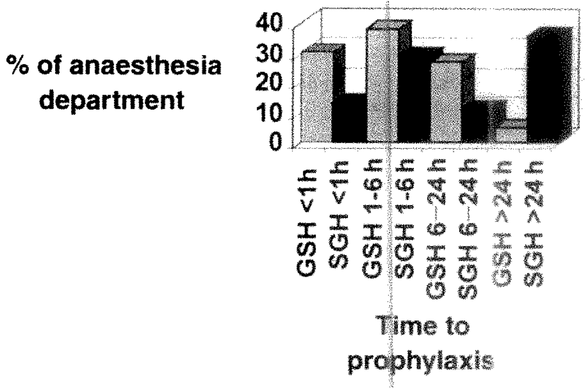

Fig 1 Recommended time to first dose of prophylaxis (correct <1 h).

2. Which of the following fluids (when not blood stained) are 'high risk' for the transmission of HIV: CSF, synovial fluid, pleural fluid, peritoneal fluid, faeces, urine, vomit, breast milk, saliva?
Answer: CSF, synovial fluid, pleural fluid, peritoneal fluid, breast milk
GSH 8% correct SGH 34% correct
3. Who should be contacted in the event of a needlestick injury?
Answer: Casualty/Occupational health department
GSH 81% correct SGH 99% correct
4. What two first aid procedures should you perform to the needlestick site?
Answer: Promote active bleeding and wash thoroughly with soap and running water
GSH 90% correct SGH 68% correct
5. How soon after a high-risk needlestick injury should post-exposure prophylaxis commence?
Answer: Within 1 hour
GSH 33% correct SGH 15% correct

At GSH, 68% respondents said prophylaxis should be within 6 h, whereas 36% SGH respondents answered >24 h (see Figure 1).

Overall, anaesthetists working with a higher risk population were more often correct (57%) compared to those working with a lower risk population (41%) when answering this questionnaire. However, anaesthetists in the 'high risk' setting had far less theoretical knowledge of high risk fluids and 12 respondents answered incorrectly as to who should be contacted in the event of a needlestick injury. This may be due to the fact that anaesthetists at lower risk had been given an educational talk on HIV prophylaxis after needlestick injury prior to the study. Despite this, the higher risk group did have a better practical knowledge of the correct first aid procedures and when prophylaxis should be taken.

Given the implications of exposure and subsequent seroconversion, we are surprised that both departments are not better equipped with the knowledge to protect themselves. Further education can perhaps change this deficiency.

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1 Diprose P, Deakin CD, Smedley J. Ignorance of post exposure prophylaxis guidelines following HIV needlestick injury may increase the risk of seroconversion. *Br J Anaesth* 2000; **84**: 767–70

Editor,–Thank you for the opportunity to reply to Drs Bennett and Reed's interesting letter. We have no current data for the local prevalence of human immunodeficiency virus (HIV) infection within our population in Southampton. Probably the most accurate estimates of HIV prevalence within the UK come from the United Nations (www.unaids.com), showing that amongst adults aged 15–49 yrs there is an estimated prevalence of 0.11% at the end of 1999. Clearly this is much lower than the prevalence estimates for HIV infection within the population of Cape Town.

Knowledge of the timeliness of post-exposure prophylaxis (PEP) among anaesthetists at higher risk in the Groote Schuur Hospital was generally better than among their counterparts in Southampton. Nevertheless, two thirds of the anaesthetists were not aware that PEP should be received within 1 h. The poor awareness of the urgency for PEP enhances our concern about inadequate knowledge regarding HIV exposures. We find it surprising that a profession whose members rely on meticulous and careful practice should not apply the same principles to their own health care. Drs Bennett and Reed's letter emphasizes our conclusion that further education is the only way forward to try to reduce the risks to anaesthetists (and other health care workers) worldwide of sustaining HIV infection after occupational exposure to HIV.

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Oral transmucosal fentanyl citrate as a premedicant

Editor,–I would appreciate the opportunity to comment on the pilot study by Watkins and colleagues demonstrating the 'failure' of oral transmucosal fentanyl (OTF) as a premedicant in daycase surgery.[1]

To assess its potential use as a premedicant, the authors compared OTF with a placebo lollipop. It must be remembered that the placebo lollipop can itself serve as a distraction and relieve anxiety, as well as increasing the attention received from staff and improving trust.[2 3] With only 11 children in each group, I doubt that a statistically significant difference could be demonstrated between even a control (i.e. no premedicant) and an active premedicant. Using the inability to detect a difference between two very small groups as an indication of failure would surely mean that most premedicants we use would 'fail'.

As regards its analgesic properties, the authors chose to compare the opiate with a non-steroidal, and claim that the opiate was a 'failure' because it had a higher incidence of nausea and vomiting. This seems flawed on three counts; first, they compared two completely different classes of analgesic; second, they did not actually demonstrate a statistically significant difference in the incidence of vomiting between the two groups; and lastly, even with these very small numbers the authors demonstrated a statistically significant improvement in pain relief with OTF. Is this not a success?

The optimum dose of oral transmucosal fentanyl has been shown to be 15–20 μg kg^{-1},[4] not 7–10 μg kg^{-1} as used by Watkins and colleagues. Even if they had used a larger study population and managed to achieve statistical significance, why use a sub-optimum dose and then label the drug a 'failure'?

We have just completed a prospective, randomized, double-blinded placebo controlled study comparing OTF (15–20 μg kg^{-1}) with midazolam as a premedicant in children undergoing tonsillectomy. We enrolled 80 patients, and provided intra-operative i.v. fentanyl as analgesia for the midazolam group. Our data (to be submitted for publication) demonstrated no statistically significant difference in the incidence of postoperative vomiting between the two groups. The data also show that oral transmucosal fentanyl is equally effective as midazolam at producing anxiolysis and compliance with anaesthetic induction. Furthermore, OTF has certain advantages over midazolam, mainly in that it is more appealing to children, but also in that it has better emergence characteristics and, unlike midazolam, is not associated with any postoperative behavioural changes.

These findings are in keeping with previous work. Two studies exist comparing OTF with another active premedicant and each found OTF equally effective.[5 6] As regards postoperative vomiting, Epstein[7] and Dsida[8] both conducted randomized, double-blind studies in which the control groups received a placebo premedicant and intra-operative opiate (fentanyl 1–2 μg kg^{-1}). Both found no statistically significant difference in the incidence of vomiting between the OTF group and the placebo group.

We were very encouraged with our experience with oral transmucosal fentanyl, and would certainly not classify it as a 'failure'.

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Editor,–Thank you for the opportunity to respond to Dr Howell's comments on our Anaesthetic Research Society abstract.[1] Obviously the abstract format provides limited opportunity for analysis and discussion of our results.

Dr Howell makes many valid comments but we wish to emphasize the following points.

(i) A low dose (7–10 μg kg^{-1}) of oral transmucosal fentanyl citrate (OTFC) was selected for several reasons. Other trials indicate a high, dose dependent, incidence of nausea and vomiting and it has been shown that many subjective opioid effects correlate with increasing serum fentanyl levels.[2] Although OTFC 15–20 μg kg^{-1} has been suggested as the optimal dose this was based on onset time and improved sedation scores not analgesia and, in addition, was associated with an incidence of preoperative vomiting not noted with lower doses.[3] OTFC 10–15 μg kg^{-1} has been shown to have analgesic equivalence to fentanyl 2 μg kg^{-1} given intravenously,[4] and dose proportional pharmacokinetics have been demonstrated.[5] Extrapolating from this data, OTFC 7–10 μg kg^{-1} was a reasonable dose to study as an analgesic for this population. In addition, our second primary outcome measure was anxiolysis which has been demonstrated in adults with OTFC 6 µg kg^{-1}.[6]

(ii) The Declaration of Helsinki explicitly forbids the use of a placebo group if an accepted treatment exists.[7] Comparison against the best available analgesia was appropriate.

(iii) This study was performed in a fully ambulatory, highly specialized setting. Therefore results are not directly comparable with ward-based trials.

(iv) The use of OTFC was assessed as 'failed' on the grounds that the study had to be discontinued because of the high incidence of side-effects. As the trial was terminated early, study numbers are small and meaningful comment cannot be made regarding the therapeutic role of OTFC 7–10 µg kg^{-1} in these patients.

Our conclusion remains that OTFC is unsuitable for use in a fully ambulatory setting.

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Effects of succinylcholine and rocuronium on the laryngeal neuromuscular junction

Editor,–I read with interest the paper by Hemmerling and colleagues comparing the effects of succinylcholine and rocuronium on the laryngeal neuromuscular junction.[1] The technique of surface laryngeal electromyography demonstrates the intuitive fact that laryngeal muscles and their neuromuscular junction configuration are different from thumb muscles. As stated in the paper, the technique has application in detection of recurrent laryngeal nerve damage during thyroid surgery and in an otolaryngological research setting.

I feel that their conclusion that rocuronium 0.9 mg kg^{-1} cannot be recommended for use in rapid sequence induction (RSI) is not justified by their data. While the authors accept that a difference in onset times of 17 s (47 s with succinylcholine and 64 s with rocuronium) has questionable clinical relevance, they then state that the differences in duration of action justify their conclusion.

There are several problems here. First, offset times were not measured in this study. To base a conclusion of a study on a parameter not assessed in that study must be questionable. Second, the authors seem to be confusing the situation in which RSI is needed with that of a difficult or failed intubation. Historically, when RSI was developed, the non-depolarizing neuromuscular junction blockers (such as d-tubocurarine) were of slow onset, making them unsafe for the technique of RSI. The slow offset made them unsafe for a difficult airway. The depolarizing alternative (succinylcholine) was therefore the only drug to use for RSI and its fairly short duration of action was a bonus for the unexpected difficult intubation. The two situations, although they may often coexist, should not be confused, as we now have a rapid-onset non-depolarizing neuromuscular blocking drug.

I would also take issue with their conclusion that 'the return of neuromuscular transmission at the larynx to control levels after 5–10 min or 30–45 min might define whether a patient survives'. It is self-evident that 5–10 min of apnoea (with or without laryngeal neuromuscular transmission) can be as fatal as 30–45 min. The authors, having gone to great lengths to demonstrate that different muscle groups react differently, base their conclusion on offset times (not measured) presumably in diaphragm or intercostal muscles which were not the subject of the study. Their study design was such that tracheal intubation was performed without any neuromuscular junction blocker at all.

In summary, although an interesting study, they seem to base the conclusion on a parameter they did not measure, in muscles they did not assess, for a clinical situation unrelated to the experimental conditions, using a technique of intubation that avoids the issue altogether.

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1 Hemmerling TM, Schmidt J, Wolf T, Klein P, Jacobi K. Comparison of succinylcholine with two doses of rocuronium using a new method of monitoring neuromuscular block at the laryngeal muscles by surface laryngeal electromyography. *Br J Anaesth* 2000, **85**: 251–5

Editor,–Thank you for the opportunity to respond to Weinbren's letter. He raises the question as to which neuromuscular blocking drug should be used for rapid sequence induction.

Whenever rocuronium and succinylcholine have been compared in the past, there was no doubt that in a dose of more than 0.9 mg kg^{-1} rocuronium can equal the onset time of succinylcholine 1 mg kg^{-1} at the larynx.[1–4] However, the use of rocuronium 0.8 mg kg^{-1} or 1.2 mg kg^{-1} for rapid sequence induction results in times for the first twitch response (T_1/T_0) to recover to 25% of 25 and 43 min at the larynx, respectively, in comparison to 4 min for succinylcholine 1 mg kg^{-1}.[5] Rocuronium is a neuromuscular blocking drug of intermediate duration, succinylcholine has an ultra-short duration.[6] The greater variability in onset time and length of neuromuscular block produced by even higher doses of rocuronium in comparison to succinylcholine[4 5] is another factor which favours succinylcholine for rapid sequence induction.

We believe that evaluation of a neuromuscular blocking drug for rapid sequence induction without taking into account its clinical duration is not appropriate. The circumstances of most rapid sequence inductions, e.g. for Caesarean section, carry a high risk of failed intubation and 'can't intubate-can't ventilate' situations which were clearly outlined in a recent survey.[7] It seems prudent to select a neuromuscular blocking drug for rapid sequence induction not only for its short onset time but also – in the light of subsequent situations which endanger the patient's life – for a short duration of paralysis.

It is true that in our study, clinical duration was only measured at the adductor pollicis muscle. It seems, however, valid to base a conclusion not only on one's own data but on other findings The comparison of succinylcholine with neuromuscular blocking drugs of a similar onset of action, such as rocuronium and rapacuronium, for rapid sequence induction will always stir controversy.[8 9]

The authors stand by their conclusion that succinylcholine is superior to rocuronium for rapid sequence induction because of less variability in its onset and degree of block and a much shorter clinical duration.

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1 McCourt KC, Salmela L, Mirakhur RK, Carroll M, Makinen MT, Kansanaho M, Kerr C, Roest GJ, Olkkola KT. Comparison of rocuronium and suxamethonium for use during rapid sequence induction of anaesthesia. *Anaesthesia* 1998; **53**: 867–71

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9 Levy DM. Rapid sequence induction: suxamethonium or rocuronium? *Anaesthesia* 2000; **55**: 86–7

Fentanyl and midazolam anaesthesia for coronary bypass surgery

Editor,–We write concerning the paper by Barr and colleagues.[1] The authors recorded the Bispectral Index (BIS) in patients undergoing coronary bypass surgery, and found that during the operative period, 8 out of 10 patients had a BIS of >60. BIS values greater than 60 are not considered to represent adequate anaesthesia,[2] but Barr and colleagues believed that their patients were adequately anaesthetized, and thus hypothesized that these high BIS values occurred because 'BIS reflects anaesthetic depth less accurately when fentanyl and midazolam are used as anaesthetics'. We are concerned about this statement.

First, it is not certain that fentanyl and midazolam can be described as 'anaesthetics'. Indeed, the phrase 'fentanyl and midazolam anaesthesia' may represent a contradiction in terms. Studies using the isolated forearm technique (IFT) show that many patients respond to command when a midazolam and opiate combination is used. Vuylsteke and colleagues studied the IFT after induction of anaesthesia with midazolam and fentanyl and concluded that this technique 'does not prevent amnestic awareness and should be abandoned'.[3] Similarly, Russell concluded that infusions of midazolam and alfentanil for induction and maintenance of anaesthesia could only be said to provide 'general amnesia'.[4]

The authors did not find any signs of inadequate anaesthesia, but is this enough to exclude awareness? The haemodynamic parameters were stable and no mention is made of sweating or lacrimation, but these signs have been shown to correlate poorly with awareness in gynaecological surgery[4] and, as mentioned by Barr and colleagues,[1] are even less dependable during cardiopulmonary bypass. The main argument used by the authors to support their contention that anaesthesia was adequate was the lack of implicit recall. However, lack of implicit recall does not guarantee that intraoperative awareness did not occur. In Russell's study of midazolam and alfentanil infusions for gynaecological surgery, 23 out of 32 patients showed evidence of awareness (response to command), yet only three patients had any evidence of implicit recall. Although midazolam has a greater effect on explicit memory, it has also been shown to affect implicit memory.[5] [6] Moreover, it has been shown that more than 60% of patients undergoing cardiopulmonary bypass develop postoperative neurological complications.[7] It is likely that the neurological insult associated with cardiopulmonary bypass may also affect memory. Episodes of intraoperative awareness may thus not always be associated with implicit recall.

What else could the authors have done to exclude awareness? An IFT instituted during induction of anaesthesia can be used to detect response to command for the first 45 min of an anaesthetic. Alternatively, the induction technique can be altered to allow the IFT to be used later on. In our experience there is usually a delay of at least 30 min between induction of anaesthesia and the start of surgery. If a short- or medium-duration neuromuscular blocking drug is used at induction, it is likely that neuromuscular function will return prior to skin incision in most cases. If the IFT is instituted at this point, further neuromuscular blocking drugs can then be administered, so that response to command can be sought during skin incision and at sternotomy, whilst still providing acceptable operating conditions. A third possibility is to enlist the support of the surgeon, use medium-duration neuromuscular blocking drugs, and allow muscle power to return at times when patient movement would not compromise safety, to enable spontaneous patient movement if anaesthesia is inadequate.

In summary the authors have not proved that anaesthesia was adequate. It is possible that the patients were aware when the BIS was high, and if this was the case then it can be said that the BIS did accurately reflect the depth of anaesthesia.

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1 Barr G, Anderson RE, Samuelsson S, Owall A, Jakobsson JG. Fentanyl and midazolam anaesthesia for coronary bypass surgery: a clinical study of bispectral electroencephalogram analysis, drug concentrations and recall. *Br J Anaesth* 2000; **84**: 749–52

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6 Hirshman E, Passannante A, Henzler A. The effect of midazolam on implicit memory tests. *Brain Cogn* 1999; **41**: 351–64

7 Shaw PJ, Bates D, Cartlidge NE, Heaviside D, Julian DG, Shaw DA. Early neurological complications of coronary artery bypass surgery. *Br Med J* 1985; **291**: 1384–7

Editor,–We would like to thank Absalom and Nagels for raising some interesting questions as to the definition and goals of good care during cardiac surgical procedures and for the opportunity to comment on their letter. Anaesthesia is a pharmacologically induced state of cognitive and autonomic depression. Adequate depth of anaesthesia includes the inability to retrieve sensations including the experience of pain analgesia. Usually we define anaesthesia as a state of unconsciousness; but clinical experience, BIS, and Absalom and Nagels' comments demonstrate that 'loss of consciousness' does not uniquely define adequate anaesthesia. The whole discussion of awareness and monitors of depth of anaesthesia demonstrate the need for clear criteria for adequate care.

Anaesthesia is dose-related and for most anaesthetics there is not an on-off phenomenon but a gradually deepening depression of various cognitive functions with memory being one of the most fragile. The devastating experience of explicit recall during paralysis simply cannot be allowed to occur, and 'depth' monitors should provide a good margin of safety for all types of anaesthetic. Implicit recall begins a grey zone of deepening anaesthetic depth with loss of implicit recall of auditory stimuli marking the deepest anaesthesia (if we even dare to view this as a linear process). Where on this scale do we place muscular reactions to auditory commands but without implicit recall? Is this level of anaesthetic depth adequate without muscular relaxation but inadequate with paralysis? Whether or not the anaesthetic in question provides amnesia may also be crucial. Must we avoid this level of mental depression and deem it inadequate? Some see a therapeutic potential in retaining a certain level of auditory responsiveness, but this places strict demands on our ability to monitor anaesthetic depth. Our goals for adequately deep anaesthesia need to be discussed.

Cardiac anaesthesia has historically depended on high opioid doses in order to blunt the haemodynamic response to noxious stimuli and thereby reduce myocardial stress. We fully agree that opioids are not anaesthetics and must be combined with a hypnotic/anaesthetic. Droperidol was not successful as that adjunct, but the benzodiazepines have traditionally filled that role with good haemodynamic stability. Implicit awareness is relatively common with opiate/benzodiazepine 'anaesthesia' but with few complaints of problematic awareness. Benzodiazepines cause a dose-dependent depression of cognitive functions although their cognitive depressant profile differs slightly form the 'other' anaesthetics/hypnotics. Benzodiazepines cause antegrade amnesia in rather lower concentrations compared to loss of response to verbal command, as is the case for propofol. Is the lack of recall of peroperative experiences or patient complaint sufficient assurance that the experience is not a subconscious problem?

These questions have led many to use inhalation anaesthetics or propofol, but the continuing use of the opiate/benzodiazepine combination makes comparative studies with proposed depth of anaesthesia monitors such as BIS all the more important. Our patients showed no clinical signs of awareness and no spontaneous movements. They were relaxed only for intubation, admittedly with the long-acting relaxant pancuronium. Should shorter-acting relaxants be used with this type of anaesthetic?

Why not use an isolated forearm technique? We have used that technique in previous studies and it may have improved our study; however, I do not believe it has a place in routine clinical practice. I fully agree that the only conclusions we can make are:

·That no patient showed signs of awareness/awakening during surgery and that haemodynamics, skin and eyes (the 'ordinary' markers for determining depth of anaesthesia) did not signal awakening, remembering that the patients were cooled to 34°C.

·That no patient had any recall of intraoperative events on two structured interviews postoperatively.

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The management of major incidents

Editor,–I was interested to read about the experiences of Williams and Squires in relation to the aftermath of the Soho bombing[1] and would like to raise two points. However, it is not my intention to appear to criticize what was a difficult and unique set of circumstances.

First, despite the requirement of NHS trusts to practice for major incidents regularly (testing both in hospital and out of hospital plans),[2] it seems that a common theme when such events occur is the need to alter such plans in the light of real-time experiences. With this in mind, I wondered if this incident had occurred close to the last hospital-wide exercise of a major incident plan for either St Thomas' or East Grinstead Hospitals and if this influenced how events unfolded, given that some of the communication failures were a direct result of out of date information being available at the time.

Second, the authors mention the need for inter-hospital transfers and given the close proximity of other hospitals in the London area, was the interface between the hospitals, on-site management and triage of casualties at the scene, considered optimal? Have any changes been made to the planned pre-hospital management of future incidents, with the benefit of hindsight?

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1 Williams KN, Squires S Experience of a major incident alert at two hospitals: 'The Soho Bomb'. *Br J Anaesth* 2000; **85**: 322–4

2 HSG(93)24. Emergency planning in the NHS: health service arrangements for dealing with major incidents. *HMSO* 1993

Editor,–Williams[1] writes of the need for psychological and social support for victims and carers of disasters and implies that counselling should be given for all health care workers. However, individual responses to stress are often idiosyncratic. There is evidence to suggest that rather than a blanket provision of psychological support, a flexible approach targeting just those who show emerging symptoms may be more beneficial

Some believe that talking through stressful experiences may improve long-term psychological health. Military psychiatrists were amongst the first to develop this and psychological therapies such as Mitchell's Critical Incident Stress Debriefing[2] were developed. During the 1980s, the use of psychological prophylactic therapies for victims of disasters became more widespread, for example, for all hospital staff involved in caring for victims of the Hillsborough disaster.[3] However, prior to 1995, randomized controlled trials of the effectiveness of psychological debriefing had not been carried out. Comparison studies had shown that fire fighters reported that therapy helped, but that measurement of the characteristic symptoms of post-traumatic stress disorder were not different from untreated controls.[4] Psychological debriefing may also damage recipients, both through secondary exposure[5] and medicalizing normal reactions.[6] It may also fill a need in others to 'do something'.

In recent years, there have been randomized controlled trials of psychological debriefing for victims of disasters. Bisson and colleagues randomly assigned 133 adult burns victims to treatment and non-treatment groups with blinded assessment at 3 and 13 months.[7] The treatment group did little better than the control group. Mayou carried out a 3 year follow up of adult trauma victims in a randomized controlled trial of psychological debriefing.[8] The intervention group had a significantly worse outcome and Mayou concluded that it was 'not appropriate treatment' of psychological disorder. Military psychiatrists found no benefit of psychological debriefing for Gulf veterans.[9]

Much is known about the development of post-traumatic stress disorder and co-morbid depression.[10] The victims of disasters bring with them their personal ways of coping and support systems. Some victims are able to work through their experiences themselves without need of external intervention which may be detrimental. A randomized controlled trial of therapy for road traffic victims[11] suggested that a better strategy was to target psychological therapy at a later date if specific psychological problems emerge

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1 Williams KN, Squires S. Experience of a major incident alert at two hospitals: 'The Soho Bomb'. *Br J Anaesth* 2000; **85**: 322–4
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Editor,–Thank you for the opportunity to reply to the letter from Dr Shirley. Sadly the events we described are not and never will be unique. The communication failures at STH to which we referred were minor and inconsequential; and it is doubtful that repeated expensive and highly disruptive hospital-wide rehearsals would materially have improved our performance in the operating theatres. Indeed our main message was that highly trained and dedicated professionals perform even better under such circumstances; our main problems arose by failing to cater for the substantial subsequent load. The 1993 document that Dr Shirley cites has since been updated by regional documents in our area annually and repeated rehearsals occur at six-monthly intervals. The immediate call-out cascade however, for practical reasons, does not extend beyond the anaesthetic consultants on-call. At East Grinstead, regular rehearsals are held and routine procedures for tertiary referrals were followed for the admission of these patients; no problems arose. Our message here is that the potential for multi-organ failure in patients transferred to specialist units must always be considered and discussed but does not of itself constitute a contra-indication to transfer, provided injuries better treated elsewhere are either excluded or the relevant condition stabilized.

We thank Dr Pilkington for her interest and have passed her comments to those responsible for this area of patient care who might wish to continue the discussion in perhaps a more appropriate forum. We have clearly disobeyed *Montaigne* and strayed beyond our expertise, but did so only to illustrate that the substantial additional workload of such tragedies extends not only chronologically but also laterally to many areas of hospital activity.

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Book Reviews

Fundamentals of Anaesthesia and Acute Medicine. R.M. Jones, A.R. Aitkenhead, P. Foëx (series editors). *Cardiovascular Physiology* (second edition). H.-J. Priebe, K. Skarvan (editors). Published by BMJ Publishing Group, London. Pp. 383; indexed; illustrated. Price £35.00. ISBN 0-7279-1427-8.

At a research seminar in the early 1990s, a professor of cardiovascular physiology gave an excellent talk on the protective effect of the amino acid taurine in myocardial ischaemia. During discussion, he was asked about a new calcium channel that had just been described. But he knew nothing about it. Sadly, the professor has since died, from a heart attack, and taurine is not in the index of the second edition of *Cardiovascular Physiology.*

This is one of the problems with books that try to 'cover the fundamentals... in a comprehensive manner [and] emphasise recent developments': the fundamentals remain important, but there is unlikely to be room to cover them properly; meanwhile, focused research interests are discussed at length but may have faded into obscurity a few years later. Clinical anaesthetists have to know something about an awful lot; we cannot know the details of current research in anything but a small section of physiology. To me, the best approach seems to be to invest in a good basic textbook, to buy a new edition every few years, and to keep an eye on reviews in the journals. These reviews are not constrained to repeat the fundamentals, and it is easier then to meld their new (and possibly insecure) knowledge with the conventional (and probably safe) textbook knowledge.

My first test of any book on cardiovascular physiology is how it deals with afterload, a logical idea when thinking of the isolated ventricle but a difficult idea in the intact human being. On this, Skarvan (the author of the chapter as well as an editor of the book) does well. He extends this, in one of the best sections of the book, to a clear description of what determines stroke volume: a balance between the elastance of the left ventricle and the elastance of the arterial tree. It is a shame he misuses the word parameter – applying it correctly to the slope and intercept of the pressure/volume relation, but incorrectly to the various measured variables of ventricular performance.

Sykes' chapter on the pulmonary circulation, the fifth in the book, shows up many of the others. Sykes knows how to construct a chapter: make it clear at the outset what the chapter is about; then works from the simple to the complex, from the known to the unknown. It may be unfair to comment when considering a book partly written by authors who are not native English speakers, but Sykes' use of language makes reading his chapter easy. He is economical with words and his sentences flow well. He avoids the irritating abbreviations that pepper the pages of many other chapters, in which AP may mean action potential or accessory pathway, TMP means transmembrane potential but TP threshold potential, and CBF means coronary blood flow or cerebral blood flow. Would the proof-reading error of Pa_{CO_2} for Pa_{O_2} have occurred if the statement had been written explicitly, 'Classic teaching is that CBF is unchanged until oxygen tension falls below approximately 7 kPa'? The abundance of abbreviations is odd in a book coming from the BMJ Publishing Group; the *British Medical Journal* itself barely allows AIDS or NATO.

A book that aims to cover the whole of cardiovascular physiology, from cellular metabolism, through ventricular performance, to the effects of anaesthetic drugs, is bound to be somewhat repetitive. But by the fourth time nitric oxide, or theories of autoregulation, are discussed, one wonders whether the editors should have attempted some cohesion by adding cross-references. The index is only partly helpful and somewhat idiosyncratic. 'Active hyperaemia' is indexed, but not 'hyperaemia'. Neither 'excitation–contraction coupling' nor 'sarcoplasmic reticulum' is indexed. Calcium is discussed many times but indexed to only three pages. Pulse wave amplitude and velocity are not indexed but are anyway only mentioned briefly in passing.

The diagrams are well presented but there are too few of them Some complicated anatomical and physiological descriptions are difficult without visual aid. An illustrative plot of baroreflex sensitivity (heart rate *versus* systolic pressure) would have helped, especially as there is an odd error in the figure illustrating the reflex effects of vasoactive drugs, which has an electrocardiogram trace of a constant heart rate. This same figure was correct in the first edition. Many reproductions from research papers commit the common statistical sins of lack of identification of error bars, failure to give the number of experiments, and stars which one assumes indicate statistical significance but at an unidentified level to some unidentified test

This is the second edition, so there must be a market for this book. Wallace liked the first edition[1] and hoped 'that more able trainees would make use of it...'. I cannot back that recommendation. The series may be titled *Fundamentals*... but there is too much that is speculative and extremely complicated, so that it is impossible to emerge from reading some sections with any clear idea of any principles – other than that there are complicated interactions between autonomic control, autoregulation, and a host of different cellular mediators that change their actions depending on the state of the endothelium and the particular vascular bed.

It is a shame that the first chapter, which the potential purchaser is likely to sample, is the weakest. It also contains, on the first page, an excellent example of misplaced enthusiasm for technological medicine. Writing 'the ultimate success of gene therapy for the failing heart continues to be constrained by the inadequate understanding of the underlying pathophysiological events' ignores the almost complete failure so far of any gene therapy to work consistently and safely even in single locus disorders.

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1 Wallace WFM. Book review. *Br J Anaesth* 1995: 75: 825

Cardiopulmonary Bypass. Principles and Practice (second edition). G.P. Gravlee, R.F. Davis, M. Kurusz, J.R. Utley (editors) Published by Lippincott Williams and Wilkins, Philadelphia Pp. 768; indexed; illustrated. Price US$139. ISBN 0-683-30476-3.

'Cardiopulmonary bypass (CPB) by extra-corporeal circulation for open heart surgery and even replacement of the heart itself were just dreams 50 years ago. Today, after millions of total body perfusions, CPB has become a standard, widely used, low risk procedure with immense benefits to humankind We got here today by a worldwide catalytic combination of research, heterodoxy and serendipity.' These sentences, that conclude the opening historical chapter, were written by a pioneer of CPB, C. Walton Lillehei and published posthumously. Not only do these words succinctly describe how tremendously important CPB is today, despite its relative youth, but also why it became what it now is. Moreover, if one has anything more than a passing interest in the historical development of CPB, one will be richly rewarded by reading this chapter.

At 768 pages, this second edition of an established textbook is a weighty tome and I was daunted by the challenge of reading it from cover to cover. However, it proved a very worthwhile experience as it allowed me to revisit many areas of CPB that I had once explored but long neglected. Not only was it reassuring to affirm that my knowledge of some areas needed little updating but also challenging to learn that there was new knowledge that would be of value to me in the future.

Despite its undoubted value, the book is not devoid of shortcomings One of its most striking features is that it is not only multi-authored (66) but also multi-edited (4). This has led to widely diverse styles of writing that range from the objective scientific review approach, to the institutional cookbook recipe Overly harsh as this criticism may be for a book that aims to cover not only principles but also practice of CPB, there remains a definite lack of uniformity. Moreover, as stated in the preface to the first edition, there is a great deal of 'redundancy' between chapters as they have been written, according to the intention of the editors, as stand-alone pieces. This approach has led to much duplication of information throughout the book and means that reading it is not an efficient means of gaining an overview of CPB. More rigorous editing might have shortened the text by a quarter and improved the overall clarity of the subject. Further, although the text is extensively indexed, there are some surprising omissions. Most striking is the singularly important religious impediment to CPB, that is being a Jehovah's Witness, which is discussed in two chapters but not indexed.

Given that all but a few of the authors are from the USA, some of the practical aspects reflect a very American approach. Whilst one's interpretation can compensate for any resulting bias that may be evident during reading, it is a niggling irritation that such things as biochemical concentrations are supplied in US units of measurement without the courtesy of providing SI equivalents for readers elsewhere in the world. Finally, although the topic is broached in a few chapters, one devoted exclusively to the benefits and drawbacks of off-pump coronary artery surgery, given its current vogue, would have been timely.

Whatever its limitations, this book is an outstanding source of information for anyone, be they anaesthetist, perfusionist or surgeon, who is interested in CPB. Not only are the book's editors well respected in the field of CPB but many of the 35 chapters are written by authorities on their chosen topics. Moreover, the up-to-date text is well laid out, supplemented with very clear figures and tables, and exhaustively referenced. All one has to do is pick a topic, find the appropriate chapter and, by reading it, one will gain a current overview of the subject as well as be pointed in the direction of suitable references for further reading. An extremely valuable feature of the end of each chapter is the section that lists the key points. This may be read last to reinforce the most important points of the chapter or, alternatively, first to decide if it is worthwhile to proceed further.

The book has five sections: equipment, physiology and pathology, haematology and clinical applications. Whilst the opening section may not be the section that many may choose to read first, it well places current practice in its historical context. For those like myself who are not perfusionists, much of my understanding of the practical nature of CPB stems from many years of exposure to different techniques and, in my case, in several different institutions around the world. The equipment and clinical application sections of this book allow one insight into the many practical aspects of CPB not only in a far shorter time but also in the one place. CPB must be the most major form of physiological trespass that is routinely undertaken around the world. This aspect is well represented by the many chapters in the physiology and pathology sections which encompass the systemic effects of CPB as well as its effects upon individual organs and systems. Haematology, given the complexity of effects both required for and induced by CPB, rightly merits its own section. As far as individual chapters, there are too many to even list the excellent chapters, far less discuss them

This is clearly not a book for a novice to CPB nor for anyone who requires an overview of the subject. However, for anyone more involved in CPB, and from whatever speciality they approach, this book is an invaluable resource. Moreover, this book should be on the library 'buy list' of any institution that undertakes CPB.

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Port-Access™ Cardiac Surgery for the Anesthesiologist. CD ROM. R. Ortega, H. Arkoff. Version 1.0 October 1997.

This is an interesting and educational CD, which aims to give the cardiac anaesthetist an insight into the world of Port-Access™ surgery. The program requires an IBM compatible PC and most modern systems will be able to run the software. Quicktime for Windows is required and is included on the CD.

The CD is divided into five chapters. The introduction is a brief verbal presentation by Dr Shemin from the University of Boston, USA, where this CD has been made. He stresses that Port Access technology is new and still under intense investigation. There are skills required of the anaesthetist in carrying out anaesthesia for Port-Access™ Surgery, which they may not be familiar with, such as percutaneous placement of a coronary sinus catheter or a pulmonary vent catheter. Although all the skills required could be easily learned they do require that the anaesthetist is an accomplished echocardiographer. The next chapter gives an overview of the surgical aspects of Port-Access™ surgery with short video clips of harvesting of the internal mammary artery (IMA), IMA anastomosis, mitral valve exposure and suturing of a mitral valve. This is followed by a chapter giving a detailed description of the five catheters used to facilitate Port-Access™ surgery. There are a number of video clips of the transoesophageal electrocardiography (TOE) and fluoroscopy images obtained during placement of the catheters. The net chapter gives guidelines for the anaesthetist. The topics include the choice of drugs, the use of a double lumen tube, the position of defibrillator pads and the choice of analgesia. A link from here to the previous chapter enables the viewer to recap on the techniques required for catheter placement. The final chapter is a video library containing over 80 short video clips about Port-Access™ surgery. This includes not only the TOE images shown earlier in the CD but also clips of the surgical incision and the instruments used.

The CD does just what I suggested at the beginning of this review. It gives the viewer an insight into Port-Access™ surgery. It is in no way comprehensive and trying to teach placement of an endocoronary sinus catheter using short video clips is rather like suggesting it might be possible to learn to ride a bike by watching a video. Recent papers about the technique emphasize how there is a very steep learning curve for the anaesthetist who is involved in Port Access surgery. There is no mention of this anywhere.

For practising cardiac anaesthetists, who want to know what some of their colleagues get up to, half an hour spent browsing through this CD would be time well spent. Do it one day during bypass.

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Evidence Based Resource in Anaesthesia and Analgesia. M. Tramèr (editor). Published by BMJ Books, London. Pp. 22; indexed; illustrated. Price £30. ISBN 0-7279-1437-5.

This is a brave book! It opens with a robust critique of evidence-based medicine (EBM). The first chapter, by Neville Goodman, articulates the concerns that many clinicians harbour concerning EBM He makes the point that for many doctors the term 'evidence-based medicine' is an implicit insult that suggests that their current practice is not evidence based. However, Goodman does not write to dismiss EBM, but to point out its limits. He reminds us that medicine has many 'grey zones' where the available data do not give a clear answer about the best way to manage a patient and concludes that EBM has much to teach us, but that it will not provide all of the answers.

The remaining three chapters in Part I of the book are concerned with the methods used in EBM. Chapter two, by Halpern, Jadad and Choi, offers an overview of randomized controlled trials, systematic reviews and clinical guidelines in anaesthesia. There are useful references to EBM resources. This chapter is heir to some of the faults described by Goodman Statements such as 'Although the specialty of anaesthesia has traditionally lagged in the development of its evidence base, the situation will likely improve' are probably not intended to cause offence, but may well do so.

The third and fourth chapters are concerned with methodology. Chapter three, by Egger and Davey Smith, explains how the pooling of data in a meta-analysis may clarify the evidence on a specific question, and offers a lucid account of the limitations of meta-analysis and how these may be addressed. Sadly, this excellent essay also contains statements that will offend those whom it should be courting. To say that 'the classic narrative review is subjective and therefore subject to bias and error' is to forget that there may be much to be learnt from the considered opinion of an expert, especially in what Goodman terms the grey-zones of medicine. The fourth chapter, by Andrew Moore, gives an elegant account of the techniques of systematic review and emphasizes that information and knowledge are not enough for the practice of medicine. Wisdom is also necessary!

The second half of the book examines areas where the techniques of EBM have been applied to anaesthesia with valuable results. The chapter on acute pain by McQuay discusses systematic reviews of postoperative analgesia. It is an example of EBM at its best. Detailed systematic reviews are used to address a complex clinical problem, that of providing the best possible post-operative analgesia for our patients. Chapter six by Møiniche and Dahl examines a number of important systematic reviews of acute pain treatment in detail. The topics covered, such as pre-emptive analgesia and the use of incisional local anaesthesia, are directly relevant to clinical practice. In chapter seven the use of intra-articular morphine is reviewed by Kelso Chapter eight, by Tramèr, gives a valuable overview of systematic reviews in PONV and chapter nine presents systematic reviews of the International Study of Perioperative Transfusion (ISPOT) techniques to reduce allogenic blood transfusion.

This book examines a number of important methodological issues, and explains them clearly by discussing them in the context of clinical questions. The implications of the outcome rate in the control group of a trial (the control event rate) is made clear in the chapter on PONV by Tramèr. The importance of internal validity in studies of analgesics, and the relevance of confirming such validity by having a third limb in such studies is explained by Kelso. The value and relevance of comparing drugs to placebo controls is clear both from the chapter by McQuay and that by Tramèr.

This book does not set out to be comprehensive, but there are important omissions. Neither the controversy surrounding the systematic review of the value of albumin in critically ill patients, nor that which followed the systematic review of fluid resuscitation with colloids as opposed to crystalloids are discussed. Both are important and controversial examples of the application of EBM to anaesthesia and should have a place in this book.

This little book is neither a textbook nor a comprehensive reference book. It is a set of personal essays about EBM and anaesthesia by leading workers in the field. Its strength is that it begins with a robust critique of EBM, but it is able to leave the reader feeling that EBM is a useful tool that has much to offer us. I commend it to all anaesthetists who wish to think about how we use research data to inform our practice

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Anesthesiology and the Academic Medical Center· Place and Promise at the Start of the New Millennium International Anesthesiology Clinics Series. Volume 38, Number 2, Spring 2000. Joseph Gerald Reves and Nicholas M. Greene Published by Lippincott Williams and Wilkins, Philadelphia. Pp. 180; indexed. Price US$66. ISSN 0020-5907.

This book is a curious hybrid. It incorporates some material written 25 yr ago by Greene and published under the title *Anesthesiology and the University.* Greene has been joined by Reves to produce an up-to-date history of academic anaesthesiology, a review of the current position, and speculations on the future development of the specialty. There is no doubt about the qualities of the authors, Greene's outstanding contribution to anaesthesia is well known and Reves is the current chairman of a department of international repute

The authors are concerned solely with the USA and an international perspective is not provided. The main chapters are entitled: attaining critical mass (1975–1990); the present (1990–2000), departmental structure, function and leadership; relationships of anaesthesiology and the academic medical centre; and the future (2000–2025). The chapter on attaining critical mass (1975–1990) was of particular personal interest and the authors seem to view this time as the golden era for academic anaesthesiology. The financial constraints imposed by managed care loom large in the chapter on the present (1990–2000) and the emphasis on departmental income and financial distribution will seem out of place to academics in the UK who have been expected to produce something out of nothing for many years. I have to confess to a feeling of *schadenfreude.* The future (2000–2025) holds few terrors if it follows the innovations outlined in the chapter, although I remain unconvinced that pharmacokinetics have any useful role in anaesthesia.

The chapter on the relationship of anaesthesiology and the academic medical centre emphasizes the need for anaesthetists to infiltrate all aspects of medical school life. The message is clear, do not hide away, get out and make a nuisance of yourself – networking by another name. However, personal experience suggests that you should avoid anything to do with the car parking arrangements if you wish to remain on speaking terms with colleagues. Departmental structure, function and leadership is heavily biased towards financial matters but contains a list of the ideal characteristics of a successful modern chairman This jewel is as follows:

An unblemished personal character
An effective leader
A successful manager
A visionary and futurist
A risk taker
A team player and team organizer

A systems thinker (looks beyond the department)
A clear communicator
A good listener
An appropriate delegator
An optimist.

I have never met anybody who fulfils these characteristics and do not expect to do so in this life. I cannot believe that our transatlantic colleagues take this list seriously, unless their grip on reality is slipping. The chapter finishes with how to deal with conflict as a chairman: 'Conflict, which inevitably arises, is adjudicated in a timely and fair manner. Systematic detractors and/or cynics of consensually developed plans will be asked to leave, since these individuals sow the seeds of general discontent when a harvest of happiness is imminent' (p. 118). So now you know, if you agree with the boss all is well. If not, then you are down the Job Centre. As a hardened cynic of many years standing I have found that a large dose of reality is the only way to curb the wilder excesses of some of our colleagues, whether they be in academia, clinical practice, management or medical politics. The stifling of vigorous debate is the road to ruin and not the road to a harvest of happiness. If the idea is good it will withstand rigorous analysis and we detractors and/or cynics will crawl away defeated.

These criticisms must be seen in the light of the intended audience and the book contains a large amount of information on academic anaesthesiology in the USA. The authors have worked hard to provide a useful resource for anaesthesiologists and it will be of value when arguing their case with the academic medical centres. I am away to look for the harvest of happiness.

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History of Anaesthesia Through Postage Stamps. Alistair G. McKenzie. Published by McLean Dubois, Edinburgh. Pp. 146. Price £9.50. ISBN 0-9514470-9-2.

A connection between anaesthesia and postage stamps is not immediately obvious, but Alistair McKenzie has combined his job as a consultant anaesthetist with his hobby of philately, and produced an unusual and probably unique book. The use of stamps for commemorations has been going on for over 100 y and the number has increased within the last 50 y or so. The author has reproduced over 350 stamps from all over the world connected with the history of anaesthesia and associated disciplines which include chemistry, physics, and physiology to mention only a few.

The book is divided into 17 chapters, each containing a concise history, with references, and is followed by black and white illustrations of related stamps. There are also, as appendices, a chronological table of outstanding events and an alphabetical list of the names commemorated on the stamps. There are even suggestions for possible future issues; for example, the year 2004 is the sesquicentenary of the removal of the Broad Street pump handle by John Snow.

Although the net is spread widely the author would probably not claim that this is a comprehensive history; given the concise approach and the fact that stamps do not commemorate everything, some omissions are inevitable. The references, however, are excellent.

The frontispiece shows eight stamps in colour. This prompts some regret that they are not all thus treated as some of the black and white copies have reproduced a bit darkly; but I suppose it was not an economic proposition.

This is an enjoyable book to dip into. It is packed with information and is clearly the result of a good deal of hard work.

P. M. E. Drury
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British Journal of Anaesthesia **85** (6): 947 (2000)

Errata

Pharmakokinetics of rectal paracetamol after repeated dosing in children (BJA 2000; 85: 512–519)

The equation on page 513 column 2 and the legend to Figure 4 should read as follows:

$$C(t) = \frac{FD}{V_d} * \frac{k_a}{k_a - k_e} * \left[\frac{(1 - e^{-nk_e\tau})}{(1 - e^{-k_e\tau})} * e^{-k_e(t - T_{lag})} - \frac{(1 - e^{-nk_a\tau})}{(1 - e^{-k_a\tau})} * e^{-k_a(t - T_{lag})} \right]$$

Editorial II. Airway devices: where now and where to? (BJA 2000; 85: 504–505)

The name of the company in the footnote was spelt incorrectly. The footnote should read:

LMA® is the property of Intavent Limited.

The publisher apologizes for these errors.

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Guide to Contributors

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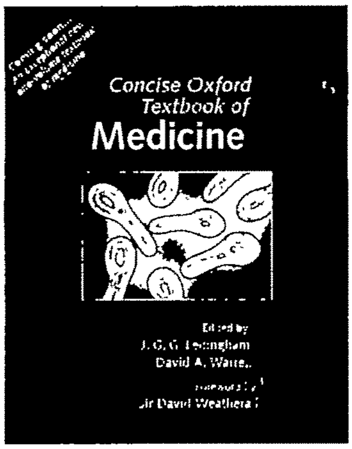

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